Evaluation of Population-Based Genomic Screening Programs in an Integrated Health System Utilizing the RE-AIM Framework

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Abstract

Background: Population-based genomic screening has the potential of improving ascertainment of individuals at increased risk for severe but clinically actionable conditions. However, the clinical utility and public health impact of population genomics-based screening will depend upon the context in which the screening occurs and how it is implemented. Geisinger in central Pennsylvania is conducting population-based genomic screening in multiple contexts: the MyCode Genomic Screening and Counseling (GSC) program that returns medically actionable genomic results to MyCode biobank participants and the PopHealth clinical screening program that offers screening as part of primary care.

Public Health Significance: Evaluation of these programs will provide evidence for the clinical utility of population genomics-based screening, as well as generate insights for successful implementation of such programs in the real world.

Methods: To understand the impact and utility of population screening as a whole, a comprehensive program evaluation was conducted across these different contexts using the RE-AIM framework.

Results: 68% (215,078/315,392) of approached Geisinger patients enrolled in the MyCode biobank and were eligible to receive actionable genomic results. A number of studies conducted and published by the GSC team have showed that the program was able to identify at-risk individuals who did not have clinical indication for testing and facilitate risk management. The PopHealth clinical screening program has been implemented in 3 primary care and specialty clinics, however, only 32.7% (56/171) the eligible providers in the pilot clinics have ordered the test for patients, and fewer have ordered the test consistently.

Conclusion: A majority of Geisinger patients were willing to participate in population genomics screening in the research setting, and most patients who received a medically actionable result followed-up with risk-management procedures. Our results have demonstrated the feasibility of integrating population-based genomic screening in the clinical context, yet many knowledge gaps remained about providers' adoption and implementation of the program, as well as whether the program can be sustainably implemented in the long term.

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Preface

I would like to thank my supervisors on this project, Dr. Alanna Rahm, Dr. Laney Jones, Cara McCormick and Dr. Tasha Strande, as well as my mentors in the MPH program, Dr. Andrea Durst and Dr. Candace Krammerer. Your guidance was invaluable and without it this work would not have been possible. I would also like to say thank you to my family and friends who have supported me throughout the research process and who encouraged me to pursue a career in public health genetics. Finally, I would like to thank everyone who participated in the genomic screening programs and helped us advance our knowledge about this new genomic application.

1.0 Introduction

As our understanding of the genomic influence on health and diseases accumulates, and the technologies for assessing genomic information continue to advance, there is growing expectation for using genomic information to benefit clinical care. Many diagnostic, therapeutic or preventative uses of genomic information have been proposed, yet few have been implemented in routine clinical practice[1]. The lag in clinical adoption of genomic medicine applications can be partially attributed to limited evidence of their clinical benefit as well as implementation issues and strategies[1,2]. This gap highlights the need for increased research efforts in building the evidence base for implementing genomic medicine applications, and integrating evidence-based applications into practice.

One genomic medicine application that has garnered much interest in moving into clinical practice is population-based genomic screening. Population-based genomic screening, as defined by the Roundtable on Genomics and Precision Health of the National Academy of Sciences, Engineering, and Medicine, is the practice of "examining genomic variants in unselected populations in order to identify individuals who are at an increased risk for a particular health concern (e.g., diseases, adverse drug outcomes) and who might benefit from clinical interventions"[3]. It is estimated that approximately 1-3.5% of the general population in the US carry one of the known genetic variants that convey risk for a serious yet treatable condition, such as hereditary cancer or cardiovascular disease[4,5]. Knowledge of their carrier status of the variants will help at-risk individuals with clinical decision-making and facilitate uptake of appropriate preventative measures, ultimately reducing morbidity and mortality[6,7]. Under current guidelines, genetic testing for these variants is only prompted when there is sufficient individual or family

medical history to suggest an underlying genetic cause (i.e. indication-based screening)[8,9]. Recent studies have found that indication-based screening will likely miss 35-90% of the individuals at risk for these genetic conditions[5,10,11]. Therefore, screening unselected adult populations for disease-causing genomic variants as part of primary care (i.e. population-based screening) has been proposed as an additional approach for ascertaining individuals who are at risk for serious health conditions but otherwise would not come to clinical attention[6,7].

Despite its potential in disease prevention, population-based genomic screening has not been widely accepted for clinical adoption due to inadequate evidence about its health benefits and possible harms. There is also much to be determined about the practice's feasibility, optimal implementation strategy, and long-term sustainability[12,13]. Some of the important knowledge gaps include: which genes and variants should be screened and with what technology, what are the best practices for returning the screening results to participants and their providers, what are the short-term and long-term clinical outcomes, what are the cost and cost-effectiveness, does it address and/or create health disparities, among many others.

Several health systems and population-based research biobanks have piloted genomic screening programs in order to generate insights critical to bridging the evidence gaps[10,14–16]. Early studies have shown these programs' efficacy in ascertaining individuals carrying genomic risk variants, improving risk management and facilitating early diagnoses of severe diseases[10,17–20]. However, the overall clinical utility and public health benefit of such programs are dependent on the context in which they are implemented and how they are implemented, including, but not limited to, the population reached, the personnel involved, the result(s) returned, the way results are communicated, and the extent to which individuals understand and incorporate the results into their care. So far, limited attention has been paid to these contextual and implementation factors,

and how these factors influence overall program outcomes. Evaluating the programs that have been implemented by including process and implementation outcomes will enable us to better understand the generalizability of their findings and overall public health impact. It will also help us identify factors and strategies that impede or facilitate the implementation of population-based genomic screening programs, therefore accelerating the development of evidence-based implementation strategies and guidelines.

Implementation science - the study of methods for promoting the integration of research findings and evidence into health practice - provides the tools (theories, models and frameworks) for measuring implementation outcomes and understanding the real-world effectiveness of health intervention programs[21–23]. One useful implementation science framework that has been used extensively for evaluating health intervention programs is the RE-AIM program planning and evaluation framework[24,25]. RE-AIM focuses on both the internal and external validity of the target health intervention program and guides the systematic reporting of program outcomes along the 5 dimensions- Reach, Effectiveness, Adoption, Implementation and Maintenance- related to determining the overall public health impact of a program.

The goal of this project is to conduct a RE-AIM program evaluation of different population-based genomic screening programs at Geisinger. Geisinger is an integrated health system located in central and northeastern Pennsylvania. Since 2014, Geisinger has established the MyCode Genomic Screening and Counseling (GSC) program, which screens for and returns medically actionable genomic variants to MyCode research biobank participants[26]. The GSC has been extended to the clinical setting through the PopHealth pilot clinical screening program, where genomic screening is offered to patients in primary care and specialty clinics as part of routine preventative care[27,28].

Since MyCode GSC and PopHealth operate under a similar genomic screening model but are implemented in different spaces (research vs. clinical setting), the two programs generate complementary evidence related to the implementation of population-based genomic screening in an integrated health system. We sought to evaluate the programs as a whole, by describing and synthesizing the data generated from MyCode GSC and PopHealth that could best inform the potential reach, effectiveness, adoption, implementation and maintenance of population-based genomic screening as a single practice.

2.0 Background

2.1 Current Implementation State of Population-based Genomic Screening

Although population-based genomic screening has not been implemented broadly as a routine clinical practice, a number of pilot programs have been launched in the past several years in order to gather more evidence about the potential clinical utility and public health impact of the practice. However, to date there is no consensus or practice guidelines on how such programs should be implemented. Programs that have been launched vary in many aspects of their practice, including the implementation context, the population engaged, the genes and variants screened, and the strategy for returning screening results[29]. This section briefly summarizes key aspects regarding the implementation of population-based genomic screening with examples of current pilot programs.

2.1.1 Implementation Context

Existing population-based biobanks - usually established by academic research hospitals, integrated health systems or national institutions - are the most common setting for implementing population-based genomic screening pilot programs. The primary purpose of such biobanks is to empower large-scale genomic discovery research, and in order to do so, the biobanks collect and store large quantities of DNA samples along with a wealth of phenotypic information from voluntary participants.

Several enabling factors make biobanks the ideal environment for piloting population-based genomic screening programs. First, biobanks contain a large quantity of genotyped/ sequenced DNA samples and are usually already equipped with the data storage and transmission infrastructure to handle the large amount of data associated with genomic screening. Moreover, participants enrolled in biobanks for general discovery research are typically unselected in terms of personal or family medical history, resembling the target population for population-based genomic screening. Finally, some of these biobanks are built with or have added on the Return-of-Results (RoR) infrastructure that allows the re-association of DNA samples with the participants' identity and electronic health records (EHR), enabling the returning of actionable genomic results to specific participants, as well as tracking and assessing their clinical outcomes[26,30–32].

Examples of biobanks in the US that have implemented genomic screening/return of results include the Partner's HealthCare Biobank at Mass General/Brigham[33], the Northwest Institute for Genomic Medicine Biorepository at Kaiser Permanente Washington/University of Washington (KPWA/UW)[34,35], the BioMe Biobank at Mount Sinai[14], the MyCode Community Health Initiative at Geisinger[26,36], as well as states-run projects like the Healthy Nevada Project[10,37] and the Alabama Genomic Health Initiative[15]. Globally, countries like the UK, Finland, Estonia, Japan and Qatar are taking national initiatives in building biobanks for precision health and genomic medicine research that also offer return of genomic results to participants[38].

More recently, academic hospitals and health systems have also begun to pilot population-based genomic screening programs in the clinical context. In these programs, participants are prospectively recruited specifically for genomic screening, usually from primary care (sometimes specialty) clinics through their healthcare providers[32]. Several study sites in the electronic MEdical Records and GEnomics (eMERGE) phase III trial (a National Human Genome Research Institute

(NHGRI)-funded study across 10 clinical sites that aims to develop methods for returning genomic results to participants)[29,31,32] have employed this model for their programs, including Northwestern University[39], Vanderbilt University Medical Center[40] and Columbia University Medical Center/ New York Presbyterian Hospital[41]. Another example of a clinically-implemented population-based genomic screening program is the DNA10K program at NorthShore University Health System[42]. In DNA10K, genomic screening is offered by primary care providers as a part of routine care in the clinics of family medicine, internal medicine and obstetrics/gynecology[43]. Given the ultimate prospect of population-based genomic screening is to incorporate it into routine primary care, these clinic-based programs provide the opportunity for exploring the feasibility of clinical implementation as well as the engagement of healthcare providers in delivering such programs.

The participants in current pilot population genomic screening programs often reflect the populations served by the hospitals or health systems in which the programs are located, and are often enriched in populations that historically have greater representation in biomedical studies[29]. For example, over 99% of the participants in the first sequenced cohort of MyCode were self-reported non-Hispanic, European ancestry[19], and over 70% of the participants in the eMERGE III cohort were self-reported Caucasian[31]. The lack of diversity will impede our understanding of how to best tailor genomic screening for diverse populations. Programs are trying to address this issue by increasing engagement with under-represented populations. For instance, Columbia's program has a targeted recruitment arm (n = 500) for populations with Latinx and/or Ashkenazi Jewish ancestry[41], and KPWA/UW's clinical-based arm (n = 500) is targeted for participants with Asian ancestry[32]. Some newer programs, such as the BioMe biobank at Mount Sinai[14] and the All of Us research program[16], are further prioritizing the recruitment of participants from diverse racial/ ethnic backgrounds.

2.1.2 Selection of Genes for Population Screening

Most pilot population genomic screening programs have opted to screen for variants in the lists of genes that the American College of Medicine Genetics and Genomics (ACMG) has deemed as medically actionable for reporting secondary findings*(ACMG SF or ACMG SF v2.0, see complete lists in Appendix Table 1)[45,46]. A gene is considered to be medically actionable if it is highly penetrant for a condition (i.e. individuals carrying particular variants in that gene have a high probability of developing the condition) which has serious health implications, and for which established medical interventions exist to substantially mitigate the health risk[6]. The second version of ACMG Secondary Findings gene list (ACMG SF v2.0) included 59 genes that are associated with hereditary cancers, cardiovascular diseases, and other serious yet treatable conditions[46]. Some programs have developed their own lists of genes to include in screening, which are usually inclusive of ACMG SF v2.0 with additional genes selected by each program according to the expected prevalence of certain genomic risks in their populations[14,31,32].

A subset of the ACMG SF genes that are associated with the three conditions meeting the CDC's Office of Genomics and Precision Public Health (OGPPH)'s criteria for having "Tier 1" evidence for clinical and public health implementation[47,48] have been widely considered as core candidates for population screening[6] - namely, the genes associated with hereditary breast and ovarian cancer (HBOC) syndrome (*BRCA1*, *BRCA2*), Lynch syndrome (DNA mismatch repair genes- *MLH1, MSH2, MSH6* and *PMS2*) and familial hypercholesterolemia (*LDLR, APOB* and *PCSK9*)(Appendix Table 1)[49]. Compared to other genes on the ACMG SF lists, the CDC Tier 1

*ACMG has recently released secondary findings list v3.0[44]. The lists of genes for screening by current genomic screening programs are expected to be updated accordingly soon.

genes are better understood in terms of their disease associations and risk mitigation strategies, and are thus given priority for implementation and assessment by many programs[10,19].

However, caution needs to be paid when applying ACMG SF or CDC Tier 1 lists of genes in the context of population screening. The ACMG SF lists of genes were developed specifically for returning secondary findings in patients who have undergone *clinical* sequencing (usually for a diagnostic or pharmacogenetic purpose) and have not been validated for population-based screening[50]. The clinical utility of screening CDC Tier 1 genes has only been established in populations that have personal or family medical history to suggest the underlying genetic conditions[9,51,52]. The ACMG has recently issued a statement citing the classic Wilson-Jungner principles for disease screening[53] (Table 1) and argues that current evidence is insufficient to demonstrate fulfillment of the 10 criteria for screening ACMG SF or CDC Tier 1 genes in the general population[54]. The key data gap lies in article no.7- the "natural history of the condition" (Table 1). The natural history of genetic conditions should include "penetrance" (i.e. the proportion of individuals with a particular genetic risk who show associated clinical manifestations, the expressivity, and the age of onset); yet we currently have incomplete understanding of the penetrance of risk variants in populations unselected by family history or clinical presentations of the diseases[54]. Given the lower prior probability that individuals from the unselected population have the conditions, those identified as pathogenic variant carriers might not experience the associated diseases in their lifetime despite the genetic risk (i.e. non-penetrance or incomplete penetrance). In those situations, a positive genomic result could lead to unnecessary patient anxiety and over-diagnosis.

Table 1. Wilson and Jungner Criteria Modified for the Context of Genomic Screening

	Classic Wilson-Jungner Criteria[53]	**Modified criteria for Population-based genomic screening**[54]
1	The condition sought should be an important health problem.	Screening should focus on genomic risk(s) for serious health problems.
2	There should be an accepted treatment for patients with recognized disease.	Options for evidence-based clinical actions should be communicated to patients in whom the genomic risk is identified.
3	Facilities for diagnosis and treatment should be available.	Clinical implementation strategies should be in place and available to anyone identified as having genomic risk.
4	There should be a recognizable latent or early symptomatic stage.	Screening should have the capability of identifying at-risk individuals during both pre-symptomatic and early symptomatic disease stages.
5	There should be a suitable test or examination.	The genomic screening strategy should constitute an improvement over existing strategies for risk identification and risk reduction.
6	The test should be acceptable to the population.	Proven screening applications should be available to all, but individual participation should be optional.
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood.	Anticipated *penetrance* and *expressivity* (i.e., natural history) should be understood based on data from comparable populations.
8	There should be an agreed policy on whom to treat as patients.	Consensus should exist on clinical classification and management for those patients who screen positive for genomic risk but in whom the evidence of the associated health problems is absent (i.e., nonpenetrant risk).
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.	Appropriate health economic analyses should be in place to understand programmatic costs and benefits.
10	Case-finding should be a continuing process and not a “once and for all” project.	There should exist plans for both: periodic reanalysis of DNA variants using updated information, and periodic clinical re-evaluation of individuals with nonpenetrant risk.

Expert groups have acknowledged the need for pilot studies to gather data and improve our understanding of the penetrance of genomic risk variants in unselected populations[6,12]. The Genomic and Population Health Action Collaborative (GPHAC) has recommended priority consideration for screening CDC Tier 1 genes, but pilot programs may choose to also include genes outside of the Tier 1 list based on their study population, the advancement of knowledge for the gene-condition pairs, and availability of reliable secondary clinical evaluation tests, to maximize screening yield[6].

2.1.3 Return of Results and Follow-up Care

Genomic screening programs can only be clinically beneficial if the participants receive their actionable genomic results along with appropriate follow-up care. However, there are currently no practice standards for returning genomic results identified through research programs, and many organizations are exploring the Return of Results (RoR) process independently. Most programs only report positive results (i.e. pathogenic/likely pathogenic (P/LP) variants in the medically actionable genes that are screened). Some programs also choose to return negative results (i.e. no P/LP variants identified), and to our knowledge only one program plans to return variants with uncertain significance (VUS) to a subset of consenting participants[32].

The RoR process usually involves three essential elements: disclosure to the participant, notification of their health care provider, and integration of results into the electronic health record (EHR)[29,32]. However, the timing and order of the three components may differ among programs. The most common procedure is to disclose the result to the participant first, then notify the provider and deposit the result in the EHR. Some programs choose to upload the result to EHR first, then notify the provider, and then disclose the results to the participant[29].

Genetic counselors are the preferred agents for returning the results to participants. In most programs in the eMERGE network, positive (P/LP) results are returned to participants by a genetic counselor through an in-person genetic counseling session or over the phone. Some programs have the participant's health provider to do the initial disclosure, followed by in-person genetic counseling if requested. In the programs that choose to return negative results, the negative results are usually returned by letter, with the option of speaking to a genetic counselor by phone if the participants have questions[29].

2.2 Population-based Genomic Screening Programs at Geisinger

2.2.1 Overview of Geisinger Health System

Geisinger is an integrated healthcare delivery system located in central and northeastern Pennsylvania. The system encompasses 9 hospital campuses, 2 research centers, an insurance operation, and more than 70 community-based primary and specialty clinics, serving more than 3 million residents in the area (Figure 1). Geisinger's service area is densely rural, with 29 out of 43 counties designated as rural or medically underserved areas by the US Department of Health and Human Services Health Resources and Service Administration (HRSA). The median household income in Geisinger's service area is 15.3% lower than the national average, with 13.1% of the population having household income below the poverty line (Geisinger, unpublished data). Much of the population in this area are relatively non-transient, with a large number of life-long residents and many multigeneration families.

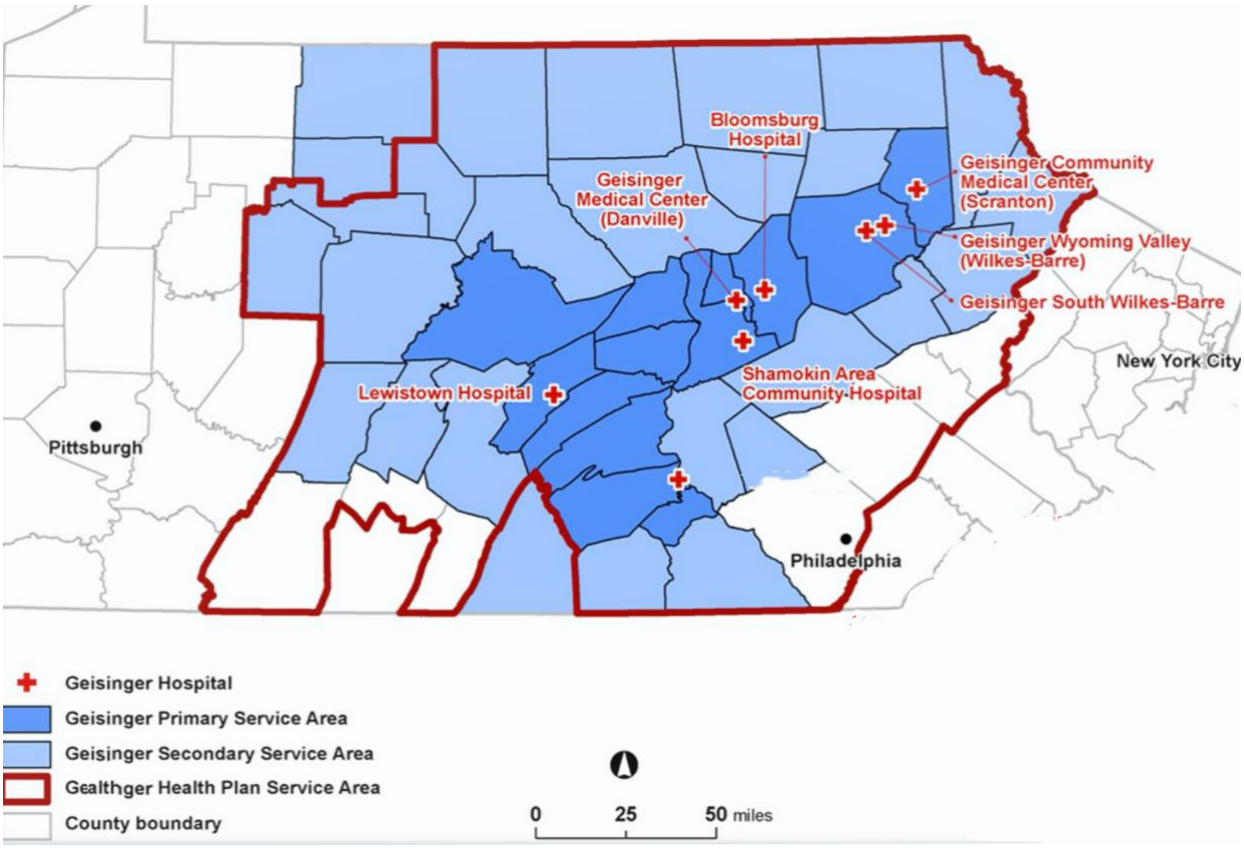


Figure 1. Geisinger Service Area. Geisinger hospital facilities include 2 tertiary/quaternary care inpatient teaching hospitals, namely the Geisinger Medical Center in Danville and Geisinger Wyoming Valley Medical Center in Wilkes Barre, and 7 community-based hospitals in Scranton, Bloomsburgh, South Wilkes-Barre, Lewistown, Gray's Woods, Jersey Shore and Shamokin area, serving an area of approximately 43 counties in central and northestern Pennsylvania.

Since 1995, Geisinger has implemented the Epic EHR system across its practice sites that now serves as the "central nervous system" for the organization, supporting everything from clinical decision making to results tracking. More than 100,000 Geisinger patients have registered to use a patient-facing online portal called "MyGeisinger" to access their health information, view laboratory test results, make appointments, and communicate with their providers[55]. Moreover, approximately 25% of the Geisinger patient population are insured by the provider owned

Geisinger Health Plan (GHP), and many of Geisinger's patients have a primary care provider (PCP) employed by Geisinger or contracted with GHP[55].

The unique combination of resources at Geisinger, including the integrated provider-insurer system, the deep-rooted trusting relationship with its patient population, and the system-wide EHR infrastructure, makes it an ideal institution for innovative healthcare delivery research[56].

2.2.2 MyCode Community Health Initiative

In 2007, as part of its effort to build a precision health and genomic medicine learning health care system, Geisinger launched a project now known as the MyCode Community Health Initiative system (MyCode) to create a biobank of serum, blood and DNA samples for health discovery research[36,56]. The overall aim of the research project is to develop methods that will enable the identification of individuals' unique biological, environmental and social influences on their health so that each patient can receive the right care tailored to their needs[13,56]. Enrollment in MyCode is open to all patients across the health system, irrespective of their age or medical history[36]. To enroll in MyCode, participants consent to provide their blood sample that can be linked to their de-identified EHRs for broad research use, and they can provide the sample whenever they have a blood draw for clinical visit[36]. To date, more than 250,000 Geisinger patients have consented to enroll in MyCode biobank, and nearly 200,000 have provided their samples[57].

In 2014, MyCode began to perform whole-exome sequencing on collected samples under the "DiscovEHR" collaboration with Regeneron Genetics Center[5]. DiscovEHR aims to combine genomic data with EHR information to uncover novel genetic associations with diseases and therapeutic targets. As of August 2020, the collaboration has sequenced 144,204 exomes, with the expectation of continuing to sequence 30,000-50,000 exomes per year[58]. The first published

DiscovEHR study reported 4.2 million single nucleotide or short insertion/deletion variants identified in the first sequenced cohort of 50,726 exomes, many of which were rare and functionally relevant[5]. Researchers are actively interrogating the associations between these variants and clinical phenotypes, seeking novel insights about the biological mechanisms and therapeutic targets for diseases.

2.2.3 Genomic Screening and Counseling Program

In the early 2010s, discussions arose among the genetic research community about the clinical utility and ethical obligation of returning medically actionable genomic results to research participants[59]. Focus groups of MyCode biobank participants showed overwhelming favor for receiving such results[60]. In October 2013, MyCode amended its consent protocol to include returning of clinically relevant findings to participants[36]. A clinical result reporting program, later named as the MyCode Genomic Screening and Counseling (GSC) program, was then established to identify medically actionable genomic results through analysis of the MyCode research sequencing data, and return the results to participants and their providers[26,56]. The GSC functionally serves as a population-based genomic screening program, for it identifies individuals with genomic risks from a population unselected for family history or clinical indication.

2.2.3.1 Genes and Variants Analyzed for Returning of Result (RoR)

The GSC program first determined a list of genes for screening and returning results through expert discussion. The first version of the gene list consisted of 76 genes for 27 conditions[26], inclusive of the initial ACMG SF list of 56 genes[45]. A reviewing process for updating the gene list was later established according to the frameworks developed by the Clinical Genome

Resource (ClinGen) for evaluating the clinical validity of gene-disease associations[61] and their medical actionability[62]. The current RoR gene list includes the 59 genes on the ACMG SF v2.0 list[46], as well as one variant in the *HFE* gene (NM_000410.3: c.845G>A, homozygous) associated with hereditary hemochromatosis (Appendix Table 1). Processes are in place for regular, systematic review of evidence so that the list is updated periodically as evidence about the gene-disease associations and their clinical implications becomes available.

As a screening program, the GSC seeks to minimize participant anxiety and healthcare overutilization caused by false positive findings. The program takes a deliberately conservative approach and utilizes a strict variant filtering and reviewing pipeline to identify variants that have the highest likelihood to be pathogenic/likely pathogenic (P/LP). Only variants that have been classified as P/LP in ClinVar with 2* or higher status[63] and pass the team's manual review for being likely to be P/LP according to the ACMG and Association of Molecular Pathology (AMP) variant assessment guideline[64] are deemed as reportable. Variants of uncertain significance (VUS) and variants with conflicting classifications in ClinVar (1* status) are excluded[65].

2.2.3.2 Participant Eligibility to Receive Clinically Confirmed Result

MyCode participants with reportable P/LP (also referred to as "positive") results generated through the analytical pipeline are re-identified to determine eligibility for clinical confirmation and disclosure of the results[65]. To be eligible to receive clinically confirmed result(s), a participant needs to be living, not have withdrawn from the MyCode biobank, have on file a signed copy of the updated consent form that specifies returning of results, and not have documentation in their EHR that shows prior identification of the variant through clinical genetic testing[65]. The participant's sample also needs to be provided after June 2015, when MyCode biobank obtained certification under Clinical Laboratory Improvement Amendments (CLIA) that allows the

processing of blood samples for clinical-grade testing[65]. Samples that meet these criteria for RoR eligibility are then sent to a CLIA-certified laboratory for Sanger confirmation.

2.2.3.3 Return of Results and Follow-up Care

After eligible variants are clinically confirmed, members of the GSC team (medical geneticists, genetic counselors and certified nurse practitioners) review the clinical reports and initiate the return of result process. Those who have a P/LP result to be returned are hereon referred to as "patient-participants". The multi-step process of retuning results to patient-participants is detailed in a previous GSC publication[26]. In brief, the process includes the sequence of (i) depositing the result into the patient-participant's EHR, (ii) notifying the patient-participant's provider through internal messaging or a provider liaison, and (iii) a series of phone calls or certified mails to disclose the result to the patient-participant and facilitate making an appointment with a GSC genetic counselor[26]. During the result disclosure genetic counseling session, the genetic counselor explains the result to the patient-participant while providing psychosocial support. The genetic counselor also reviews the patient-participant's family history and coordinates targeted clinical evaluations to assess their associated disease risks. The GSC team then refers the patient-participant for appropriate risk management procedures, tracks relevant clinical outcomes through EHR, and facilitates cascade testing for at-risk relatives[26]. The RoR process follows the principle of patient autonomy, as GSC only returns results to patient-participants who explicitly consented to RoR, and supports patient-participants' choice of whether to follow-up with a provider or disclose their results to at-risk family members[13].

As of August 2020, 92,455 out of 144,204 research-generated exome sequences have gone through the genomic screening analysis pipeline, and 1,497 medically actionable genomic results have been clinically confirmed and returned to patient-participants[66]. Early results have shown the

program's potential to ascertain individuals who carry genomic risk variants but would not be identified according to clinical genetic testing guidelines, and to facilitate risk management among these individuals in a short period after result disclosure[17–20,67–69]. However, systematic studies are needed to assess long-term outcomes and the overall clinical utility of the program.

2.2.4 PopHealth Clinical Genomic Screening Program

Given the promising results in improving preventative care for many MyCode research participants, in 2018 Geisinger initiated a pilot study (referred to as PopHealth) to implement genomic screening in the primary care setting[27,28]. Given the pivotal role that primary care providers (PCPs) play in preventative care, the PopHealth pilot program aims to engage PCPs in delivering genomic screening as a part of routine primary care to all adult individuals irrespective of disease indications. Providers in clinics selected to pilot PopHealth may order the genomic screening test for their patients with verbal consent.

The PopHealth test operates under a similar model as used for MyCode Genomic Screening and Counseling, but some aspects of PopHealth's approach are distinctive from those of MyCode GSC (Table 2). Both programs use exome sequencing to screen for P/LP variants in the medically actionable genes on the ACMG SF v2.0 list, but unlike MyCode GSC, PopHealth does not return results for the *HFE* variant[70]. Moreover, PopHealth exome sequencing is performed in a clinical laboratory with CLIA certification, which allows both positive and negative screening results to be returned[70]. As compared to GSC's deliberately conservative approach that only reports variants that have the highest likelihood to be P/LP, the variant analysis approach used by PopHealth approach will report all variants that meet the ACMG-AMP guideline for being P/LP. All positive

results from the PopHealth test are reviewed by an internal genomics team before disclosed to patients by the ordering provider or a genetic counselor. Negative results are returned as a letter.

Table 2. Key Differences Between MyCode GSC and PopHealth Clinical Screening

	MyCode GSC	**PopHealth**
Implementation context	Research biobank	Primary care clinics
Who deliver the program	Research personnel	Primary care providers
Screening model	Opportunistic	Proactive
Genes screened	ACMG SF v2.0 + *HFE* (c.845G>A)	ACMG SF v2.0
Variant reporting approach	Conservative; only reports the variants that have the highest likelihood to be pathogenic. Some P/LP variants might not be reported.	Unlikely to miss P/LP variants
Return of negative results	No	Yes

2.3 Implementation Science and Program Evaluation

Developing an evidence-based health application does not mean that it will spontaneously move into practice and lead to public health benefit. It has been widely reported that new evidence-based clinical innovations take an average of 17 years to reach routine usage, and only 14% of research discoveries ever make it to clinical practice[71,72]. Aware of the lag and lack in uptake of potentially life-saving research discoveries, a new discipline known as implementation science was developed to address the challenges in moving evidence-based interventions into practice[73].

Implementation science is defined as "the scientific study of methods for promoting the systematic dissemination and integration of research findings and evidence-based practices into

practice"[21]. Implementation science studies the tools, such as theories, models, frameworks and study designs, that can be used to (i) understand the multi-level contextual and process factors that impede or facilitate the implementation of evidence-based interventions into practice, (ii) develop strategies that overcome the barriers and enhance the facilitators of implementing the evidence-based interventions, and (iii) evaluate the implementation of the interventions[22,73,74].

2.3.1 The RE-AIM Framework

One implementation science framework that is particularly useful for program evaluation is the RE-AIM framework[24,25]. RE-AIM was developed specifically for evaluating health intervention programs with respect to both internal and external validity[24], but can also be used for program planning and reporting research to practice outcomes[25]. The framework assesses 5 key dimensions related to the potential public health impact of a given intervention program and its likelihood to be sustainably implemented in the setting(s) of interest: Reach, Effectiveness, Adoption, Implementation and Maintenance[24]. Reach refers to the individual-level uptake of the given program, which includes the absolute number, percentage, and representativeness of individuals who are willing to participate in the program. Effectiveness is the impact of the program on individuals' health outcomes, including quality of life, change in disease status, as well as economic outcomes and potential negative effects. Adoption refers to the absolute number, percentage and representativeness of settings and agents (people delivering the program) that are willing to take part in the program. Implementation is the consistency with which key elements of the programs are delivered, adaptations in the protocol, as well as the time and cost of implementing the program. Maintenance, on the setting level, is the extent to which a program becomes institutionalized as a part of routine practice. Maintenance can also be assessed on the

individual level, as the long-term effects of the program 6 months or longer after the intervention is concluded[24,25].

The RE-AIM framework has been widely used for evaluating public health and community-based health intervention programs in a variety of health promotion areas[25,75], such as aging and caregiving[76], physical activity promotion[77], HIV/AIDS intervention[78] and medication adherence[79]. RE-AIM has also been previously used for evaluating a genomic health application - a web-based, patient-facing family history collection tool for risk assessment and clinical decision support[80]. The study found that the family history collection tool was able to reach diverse patient populations and be integrated into a range of clinical care settings with fair implementation consistency[81]. However, like any genomic health applications that have only existed for a relatively short period of time, more data related to the long-term effects of the program are needed to understand the maintenance and sustainability of the practice.

3.0 Methods

3.1 Overall Study Design

This project sought to retrospectively evaluate the implementation and potential public health impact of population-based genomic screening programs in an integrated health system. We explored an array of outcomes on the participant-, provider-, clinic- and system- level. We utilized the RE-AIM program planning and evaluation framework[24,25] to guide the collection and synthesis of empirical data generated from different programs that informed potential reach, effectiveness, adoption, implementation and maintenance of population-based genomic screening as a whole. Reach and Effectiveness were evaluated using data from the MyCode biobank and the Genomic Screening and Counseling (GSC) program, because MyCode has been implemented across the health system for a longer period of time and thus has generated more evidence regarding the system-wide reach of genomic screening and its clinical utility. Adoption, Implementation and Maintenance were evaluated using data from the PopHealth clinical screening program, with the rationale that PopHealth is the next step from MyCode GSC to implementing population-based genomic screening in the primary care setting, so the Adoption and Implementation of PopHealth by clinical settings and clinical practitioners can inform us about barriers and facilitators of integrating population-based genomic screening into routine clinical practice, and how to improve the implementation of such programs moving forward.

3.2 Study Settings and Population

3.2.1 MyCode Biobank Participation and Consent

Patients throughout the Geisinger health system have been enrolled in the MyCode research biobank regardless of age or medical history[36]. Multiple avenues for MyCode enrollment are available: interested individuals can either provide their consent through the MyGeisinger online patient portal, request an appointment with a member of the MyCode research team (i.e. a consenter), or consent on site when approached by a consenter during their visit to a Geisinger clinic[82]. During the consent process, the consenter (or online form) explains that participation in MyCode is voluntary, will not impact the care they receive at Geisinger, and may not lead to direct benefit to the participants themselves[36]. By enrolling in MyCode, participants consent to provide their blood (including DNA) samples that can be linked to their de-identified EHRs for broad research use.

In October 2013, MyCode consent was amended to specify that if important information relevant to the participant's and their family's health are uncovered during research, MyCode can re-identify the participant and notify them and their providers of the finding[26]. MyCode enrollees who consented to the amended, return-of-result (RoR) consent are eligible to receive medically actionable genomic results and are thus considered participants of the population genomic screening program. Those who consented before October 2013 have been contacted periodically and encouraged to reconsent to the updated, RoR eligible consent. All protocols for MyCode recruitment and return of results were approved by the Geisinger Institutional Review Board.

3.2.2 Genomic Screening in MyCode Research Biobank Participants

Whole exome sequencing has been performed for a subset of MyCode participants through MyCode's DiscovEHR collaboration with the Regeneron Genetics Center[5,58]. The methodologies for conducting genomic screening in the research-grade exome sequencing data have been detailed in previous publications[26,65]. In brief, the program analyzes sequenced exomes in aggregate and identifies variants that have the highest likelihood to be P/LP in a subset of genes deemed as medically actionable, which include the 59 genes on the ACMG SF v2.0 list[46] plus one homozygous variant in the *HFE* gene (NM_000410.3: c.845G>A)(Appendix Table 1)[65]. Positive results are confirmed in a CLIA-certified laboratory and reviewed by the GSC team before disclosed to eligible patient-participants[26,65]. A member of the GSC team (usually a genetic counselor) calls each participant to discuss the result and coordinate genetic counseling, targeted clinical evaluation and risk management according to appropriate guidelines. The clinical evaluation may include assessment for relevant clinical manifestations, review of past medical history and condition-specific family history, which aims to both identify symptoms that may require clinical attention and gather information relevant for understanding the natural history of the disease in this unselected population[26]. The GSC team also provides informational resources for patient-participants about how to facilitate cascade testing for at-risk relatives[26].

3.2.3 Implementation of Genomic Screening in Primary Care

Since 2018, Geisinger has initiated the PopHealth pilot study that aims to implement population-based genomic screening as a part of routine primary care[27,28]. The PopHealth test is a clinical-grade exome sequencing test that screens for P/LP variants in the 59 medically actionable

genes on the ACMG SF v2.0 list[70]. Primary care clinics for piloting PopHealth were selected based on the clinics' intention to participate, as well as the clinics' size and geographic location to maximize population coverage. Training sessions were held by PopHealth research staff for providers in the pilot clinics that addressed the background of the program, the potential clinical benefit for patients, as well as the consenting and ordering process (Appendix B). Providers at these selected clinics may choose to order the screening test for any interested adult patients regardless of their disease status and family history. The test can be ordered by obtaining the participant's verbal consent and using a set of preset commands in the Epic EHR system (referred to as "SmartSet") to document the consent process and place the order.

3.3 Measures and Data Source

In order to evaluate the overall potential public health impact of population genomic screening, we devised our measures based on aspects from different programs that are the most representative of how a population-based genomic screening program would be implemented across the clinics in an integrated health system. The outcomes measured and data sources used are summarized in Table 3. The evaluation protocol was deemed as non-research by the Geisinger Institutional Review Board, and all data were obtained under an institutional Data Usage Agreement.

Table 3. RE-AIM Measures and Data Sources

Dimension	Key Measures	Data Sources
Reach Individual-level uptake of the program	- Number and percentage of eligible Geisinger patients reached by the genomic screening program - The characteristics of participants and their representativeness to the general Geisinger patient population - Reasons why individuals participate in the genomic screening program or not*	MyCode enrollment database Semi-structured interviews with participants
Effectiveness The impact of the program on individuals' health outcomes, and potential negative effects	- The program's impact on patient-participants' clinical outcomes, which includes new disease diagnoses and changes in risk management - Psychosocial outcomes related to receiving the result* - Number of at-risk relatives reached out and ascertained*	Published literature and ongoing research related to clinical utility Post-disclosure survey (3 month and 6 month)
Adoption Provider-level uptake of the program	- Number and percentage of primary care providers who offer genomic screening to patients - Characteristics of providers participated in PopHealth, and the differences of characteristics of providers who participated vs. those of providers who did not* - Motivations and barriers for participating the program*	PopHealth and institutional database Semi-structured interviews with providers
Implementation The consistency and adaptation of delivery of the program	- Consistency of delivering the program according to protocol - Adaptations in protocol over time* - Cost and time of delivering the program* - Barriers and facilitators in delivering the program*	PopHealth database Interviews with key informants
Maintenance The sustainability of the program	- Setting level: the extent to which the test is institutionalized into routine practice (even after external funding source is removed)* - Participant level: the extent to which patient-participants continue to change medical care or more change medical care over time?*	PopHealth database Interviews with key informants EHR review

*: The data collection and analyses for these measures are ongoing and complete data will not be presented in this manuscript.

3.3.1 Reach: MyCode Enrollment Data

The *Reach* of population-based genomic screening in Geisinger was defined as "the percentage of population that would participate if it was offered to them" and was operationalized as the percentage of the population who are actively enrolled in MyCode biobank and are on the consent eligible to receive genomic screening results.

We obtained de-identified information of individuals who consented or were invited to consent to MyCode biobank (as documented by MyCode consenters) over the period between February 2007 to August 2020 from the MyCode enrollment database. The individual level data included (i) demographic characteristics such as age, sex, race, ethnicity and de-identified zip code, (ii) whether the individual had a Geisinger PCP and which insurance they had, (iii) in which month/year the individual consented/declined/withdrew to/from the study and through what method, (iv) if the participant provided consent before October 2013, whether they had reconsented and when, (v) whether the participant had provided a blood sample, and (vi) the medical conditions the individual had as well as a calculated Charlson Comorbidity Index (CCI)[83]. We stratified the individuals based on their participation and consent status in MyCode biobank into 4 categories: (i) actively enrolled (had not withdrawn from the biobank as of August 2020) and RoR-eligible, (ii) actively enrolled but non-RoR eligible, (iii) declined and (iv) withdrawn. Those who were enrolled and RoR-eligible were deemed as population genomic screening participants. The control population included all other individuals documented in the MyCode enrollment database, including those who declined, withdrew or were on the non-RoR eligible consent.

All statistical analysis was performed in R. We first described the absolute number, percentage and key characteristics of the individuals who consented to population genomic

screening. We then compared characteristics of population genomic screening participants to those of the control population, as well as to the aggregated characteristics of general Geisinger patient population. The comparisons of categorical variables between groups were performed by Chi-squared test or Z-test for proportions. Non-normal continuous variables were compared using Wilcoxon rank sum test.

3.3.2 Effectiveness: Literature Review and Cataloging of Ongoing Research

In collaboration with the MyCode Genomic Screening and Counseling program leadership, it was determined that most of the *Effectiveness* evaluation questions had been addressed in previous studies or were being studied in other projects. Therefore, instead of using primary data to evaluate individual-level outcomes directly, we collated and synthesized key findings/research questions from published studies and ongoing projects that are related to the effectiveness (i.e. clinical utility) of the MyCode GSC program.

A systematic literature search was conducted in December 2020 by querying the PubMed and Google Scholar databases for any published articles and abstracts related to MyCode GSC. The search term combinations we used included: “MyCode Genomic Screening and Counseling”, “MyCode Geisinger” and “Geisinger genomic screening”. The list of articles and abstracts generated was reviewed by MyCode GSC leadership to ensure there were no missing publications. We included studies that reported findings in the following themes related to demonstrating the clinical utility of population-based genomic screening: (i) the prevalence of genomic risk variants in unselected populations, (ii) the penetrance of risk variants in individuals ascertained from unselected populations (i.e. relevant family history and disease manifestations), (iii) patient-participants’ adherence to risk management guidelines after result disclosure, (iv) patient-

participants' clinical outcomes, including relevant disease diagnoses, quality of life, morbidity and mortality, and (v) other individual-level outcomes such as the psychosocial impact of receiving the result and economic outcomes. The key findings of the included studies were summarized and coded with respect to those themes.

To understand what additional evidence is currently being generated through ongoing studies, we surveyed the MyCode GSC team using an existing spreadsheet used by program leadership to track ongoing projects related to effectiveness. The spreadsheet documented the subjects of the ongoing projects, key questions asked, population studied, and methods used. All team members were asked to review the sheet and add any updates they had on their projects.

3.3.3 Adoption, Implementation, Maintenance: PopHealth Data

Adoption, Implementation and Maintenance were assessed using the provider- and clinic-level data on PopHealth usage. We obtained information from the institutional database about the authorizing providers and the clinics for all PopHealth orders that were placed between July 2018 and December 2020.

Adoption refers to the degree of uptake of the intervention program by settings and intervention agents. Since the participating clinics of the PopHealth program were selected by institutional decision and participation is not currently open to additional clinics, setting-level adoption of the program cannot be measured at this time. Provider-level adoption was measured as the number and percentage of eligible providers who utilized the PopHealth test for their patient(s), and the number of tests ordered per provider. *Implementation* measures the intervention agents' fidelity to the key elements of the intervention program, as well as adaptations introduced throughout the course of the program. In the case of PopHealth, since the goal of the program is

to explore the delivery of genomic screening to the population as part of routine primary care irrespective of medical indications, fidelity to the protocol refers to the degree to which providers consistently offered the test to patients and whether they actually offered testing to patients without input of medical indication. In this study, consistency/fidelity was measured by number of test orders by providers over time, and the percentage of orders placed by providers using the Epic SmartSet. *Maintenance* measures the extent to which a program has been institutionalized and used sustainably over time. In this paper, Maintenance was operationalized as the number of tests ordered in pilot clinics as a function of time.

4.0 Result

4.1 Reach

Of the 315,392 Geisinger patients who were approached and invited to enroll in MyCode biobank over the period from February 2007 to August 2020, and whose information was documented in the MyCode enrollment database, 237,020 (75.2%) consented to participate in the biobank. Of the consented participants, 3,577 (1.5%) later withdrew from the study, 18,365 (7.7%) were on the non-RoR eligible consent, and 215,078 were actively enrolled with eligibility to receive results from genomic screening. Therefore, the reach of population genomic screening in Geisinger is estimated to be 215,078/315,392 (68.2%) (Figure 2).

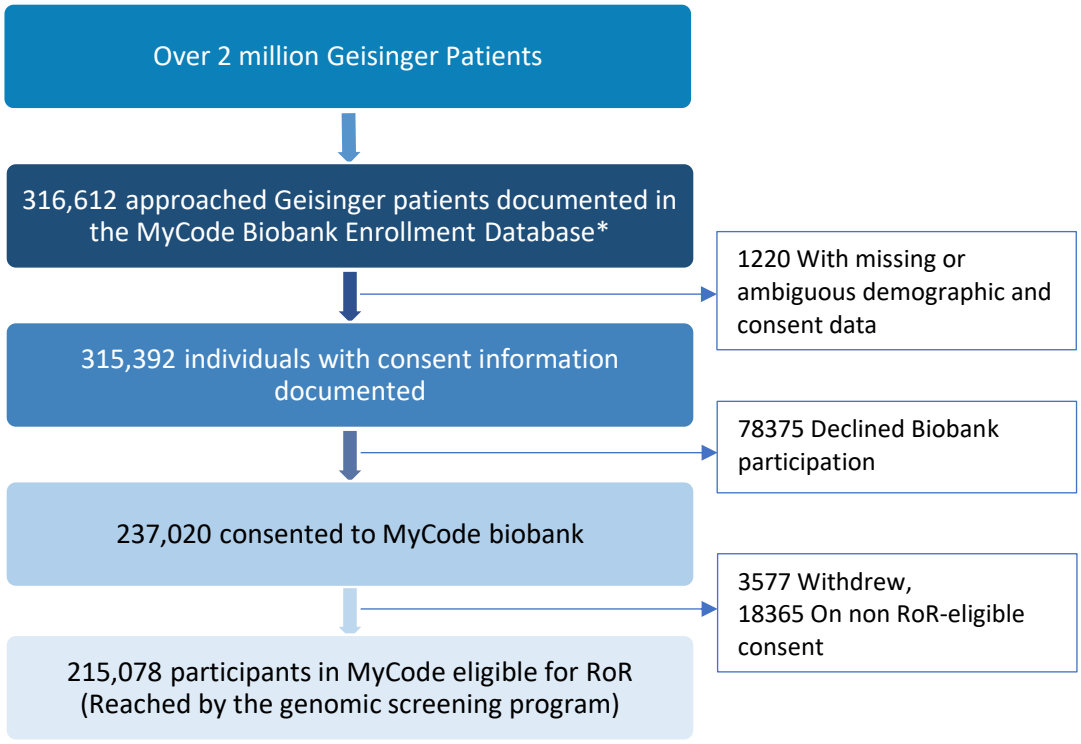


Figure 2. Number of Participants Enrolled in MyCode and Eligible for RoR

We found statistically significant differences in demographic characteristics between those who were willing to participate in MyCode genomic screening and those who did not. Compared to the population that did not participate (declined to participate in MyCode biobank, withdrew, or did not update to RoR-eligible consent), participants of genomic screening were younger (age median [IQR]: 55 [38,68] vs 57 [39,71], $p < 2.2 \times 10^{-16}$), had a greater representation of males (40.4% vs 39.7%, $p < 0.0001$), had a higher proportion of white (95.8% vs 94.2%, $p < 2.2 \times 10^{-16}$) and non-Hispanic/Latinx (96.1% vs 94.4%, $p < 2.2 \times 10^{-16}$) population (Table 4). The genomic screening population also had a higher proportion of individuals who had a Geisinger PCP (61.7% vs. 60.2%, $p<0.0001$) or were insured with Geisinger Health Plan (38.6% vs. 34.1%, $p < 2.2 \times 10^{-16}$) compared to their non-participating counterparts.

Compared to the general Geisinger patient population, participants of population genomic screening were higher in age (median [IQR]: 55 [38, 68] vs. 40, $p < 2.2 \times 10^{-16}$), had a higher proportion of female individuals (59.6% vs. 52.1%, $p < 2.2 \times 10^{-16}$) and were less diverse in terms of race and ethnicity- 95.8% of the genomic screening participants were White, and only 2.9% were Hispanic/Latinx, while 90.5% of the general Geisinger patient population were White and 5.2% were Hispanic/Latinx ($p < 2.2 \times 10^{-16}$). Compared to the Geisinger general patient population, the genomic screening participants were also more likely to have a Geisinger PCP (61.7% vs. 28.7%, $p < 2.2 \times 10^{-16}$), more likely to have insurance with GHP (38.6% vs. 21.8%, $p < 2.2 \times 10^{-16}$), and have higher Charlson Comorbidity Index (median [IQR]: 2[0,4] vs 0, $p < 2.2 \times 10^{-16}$).

Table 4. Characteristics of Participants in Population Genomic Screeening, Controls, and General Geisinger Population

	MyCode Genomic Screening (N = 215078)	Control Population* (N = 100314)	p-value†	General Geisinger Population (N = 2072639)	p-value‡
Age, median [IQR]	55 [38, 68]	57 [39, 71]	***	40 [20, 62]	***
Sex, n(%)					
Female	128149 (59.6)	60456 (60.3)	**	1079082 (52.1)	***
Male	86928 (40.4)	39850 (39.7)		993557 (47.9)	
Unknown	1 (0.0)	8 (0.0)			
Race, n(%)					
White/European Ancestry	206102 (95.8)	94487 (94.2)	***	1876010 (90.5)	***
Black/African Ancestry	5771 (2.7)	3795 (3.8)		109164 (5.3)	
Native American	278 (0.1)	132 (0.1)		2995 (0.1)	
Asian or Pacific Islander	1516 (0.7)	1515 (1.5)		36894 (1.8)	
Unknown/other	1411 (0.7)	385 (0.4)		47576 (2.3)	
Ethnicity, n(%)					
Hispanic/Latinx	6284 (2.9)	3572 (3.6)	***	107788 (5.2)	***
Not Hispanic/Latinx	206776 (96.1)	94725 (94.4)		-	
Unknown	2018 (0.9)	2017 (2.0)		-	
Has a Geisinger PCP, n(%)	132652 (61.7)	60428 (60.2)	**	594847 (28.7)	***
Insured with GHP, n(%)	82926 (38.6)	34240 (34.1)	***	451835 (21.8)	***
CCI, median [IQR]	2 [0, 4]	2 [0, 4]	***	0 [-]	***

Abbreviations: PCP, Primary Care provider; GHP, Geisinger Health Plan, CCI, Charlson Comorbidity Index; IQR, Interquartile Range.
*Control population include: individuals who declined or withdrew participation in MyCode, and participants on the non-RoR eligible consent.

† Comparison between MyCode genomic screening population and control population. Chi-squared test was performed for categorical variables with multiple levels (Sex, Race, Ethnicity). Z-test for two proportions was used for categorical variables with two levels (%Geisinger PCP, %GHP). Two-sample Wilcoxon test was used for comparing the medians for continuous variables (Age and CCI).
‡ Comparison between MyCode genomic screening population and Geisinger population. Chi-squared test was performed for categorical variables with multiple levels (Sex, Race). Z-test for one proportion was used for logistical variables or categorical variables with two levels (Sex, % Hispanic/Latinx, %Geisinger PCP, %GHP). One-sample Wilcoxon test was used for non-normal continuous variables (Age and CCI), treating the medians of the general Geisinger population as the population median.
p-value abbreviations: ***: $p < 2.2 \times 10^{-16}$, **: $p < 0.0001$

4.2 Effectiveness

The literature review on Effectiveness included six peer-reviewed articles and two abstracts published between 2016 and 2020. The complete list of reviewed studies, along with their key findings and coded themes are summarized in Appendix Table 2. All of the previous studies on effectiveness were conducted in the first sequenced cohort of MyCode participants under the DiscovEHR study (N = 50,726), or a subset of the cohort who had received a P/LP variant in one of the medically actionable conditions. All previously published studies focused on the three CDC Tier 1 conditions: three (37.5%) studies focused on familial hypercholesterolemia (FH)[17,68,84], three (37.5%) on hereditary breast and ovarian cancer syndrome (HBOC)[18,20,67], and two studies included all three Tier 1 conditions[19,85].

4.2.1 Prevalence and Penetrance of Risk Variants in Unselected Populations

Two articles and one abstract presented data on the prevalence of genomic risk variants in the population. Of the first sequenced cohort of 50,726 MyCode participants, 229 (1 in 222) were found to carry P/LP variants for FH[17] and 267 (1 in 190) were found to carry P/LP variants in BRCA1/2[20]. The prevalence of Lynch syndrome (LS) variants has not been published separately, but one abstract reported that the aggregate prevalence of risk variants for HBOC, FH and LS was 1 in 78[85], suggesting the prevalence of LS variants in this population to be 1 in 310.

Three articles reported data on the burden of relevant diseases in individuals ascertained with genomic risk variants from this unselected population (which is relevant to estimating the penetrance of the genomic risk variants in this population). Overall, 65% of the individuals identified with a risk variant in one of the Tier 1 genes had personal or family history of relevant

diseases[19]. One study found that individuals with FH variants had 69 ± 3 mg/dl greater maximum LDL-C than noncarriers and had significantly increased odds of having general (odds ratio, 2.6) and premature coronary artery disease (odds ratio, 3.7)[17]. Thirty-five percent of individuals identified with FH P/LP risk variants were deemed unlikely to have FH based on information from their EHR, suggesting that the variants carried by them might have reduced penetrance[17]. Another study reported that 21% of the individuals identified with BRCA1/2 risk variants had a prior relevant syndromic cancer diagnosis and had increased odds of having a history of breast cancer (odds ratio, 5.95) or ovarian cancer (odds ratio, 18.3) compared to non-carriers[20].

4.2.2 Ascertainment of At-risk Individuals

The published studies highlighted the program's ability to ascertain individuals at risk for serious diseases but had yet to come to clinical attention. Eighty-seven percent of the patient-participants identified with a risk variant in one of the Tier 1 genes were unaware of their genetic risk prior to receiving the MyCode result[19]. Some of these identified individuals had sufficient personal or family history to meet criteria for clinical testing but had not received referral for testing before. For example, 50.5% of the individuals without prior knowledge of their BRCA1/2 variant met National Comprehensive Cancer Network (NCCN) criteria for clinical testing but had no prior genetic testing or referral for genetic counseling documented in the EHR[20]. Moreover, none of the individuals meeting the clinical criteria for "definite" or "probable" FH diagnosis had been genetically diagnosed[17]. Together, these findings suggest that the population-based genomic screening program can help address the clinical under-ascertainment of at-risk individuals due to difficulties in applying indication-based testing guidelines.

4.2.3 Post-Disclosure Risk Management and Clinical Outcomes

Previous studies have also demonstrated the program's potential in guiding preventative care and improving clinical outcomes for at-risk individuals. Overall, 70% of the patient-participants who were eligible to have risk management had taken at least one risk management procedure within 1-3 years after result disclosure[19], but the uptake of risk management behaviors varied among conditions and the types of risk management procedures available. Among the women who received a BRCA1/2 result but did not have a previous cancer diagnosis, 49.2% had a genetic counseling visit, 50- 92.3% had a mammogram or MRI, and 11.8- 30.8% had a salpingo-oophorectomy[19,67]. Among the patient-participants who received an FH result, 82.6-100% had an LDL-C measurement via lipid panel or direct LDL test, 51.3-82.6% discussed their result with a health professional, and 39.1% had changes made to their treatment regimens[19,84]. One study also found statistically significant improvement in patients' adherence in lipid-lowering therapy (LLT) after disclosure of an FH result (76.8% post-disclosure compared to 63.9% pre-disclosure, $p < 0.01$)[68]. Another small clinical outcome study found that three individuals identified with FH who did not meet the lipid control goal (LDL-C < 100 mg/dL) before result disclosure met goal after learning their result and following appropriate risk management[84].

It was estimated that 61% of post result disclosure diagnoses of cancers and FH features could be attributed to the genetic screening result[19]. One early case series reported three cases without outstanding personal and family history of HBOC that were found to have early stage BRCA1/2-related cancers during post-disclosure risk management[18].

4.2.4 Psychosocial and Financial Outcomes

The psychosocial and financial impact of the program on patient-participants have not been extensively studied in the past literature. One qualitative study conducted semi-structured interviews with 7 patient-participants who received positive results for FH and found that most interviewed patient-participants were not surprised by their result as all of them knew they had high cholesterol and/or family history of coronary artery diseases, and some felt that the genomic result provided an answer to their personal or family history[84]. Another study analyzed the healthcare utilization and costs for patient-participants before and after receiving a P/LP BRCA1/2 result and found no statistically significant differences in healthcare utilization and average total costs of care between one-year pre- and post-disclosure periods ($18,821 vs. $19,359, $p = 0.76$)[67].

4.2.5 Ongoing Studies

We collected information on eight on-going projects relevant to the effectiveness of the MyCode GSC programs (Appendix Table 3). Most current ongoing projects are focusing on conditions outside of the CDC Tier 1 list (although one is about LS), such as endometrial tumor syndrome, familial adenomatous polyposis, and cardiac conditions. Six out of eight projects are studying the clinical manifestations and relevant family histories of individuals identified with a P/LP result via retrospective chart review in order to inform the penetrance of genomic risk variants in individuals ascertained from population screening. One study is examining patient-participants' risk management behaviors after receiving a P/LP result, and another is studying the uptake of cascade testing and participants' sharing of their results to family members.

4.3 Adoption

As of now, the PopHealth clinical genomic screening program has been made available to three Geisinger clinics or practice sites (clinic #1 since July 2018, clinic #2 since September 2018, and clinic #3 since December 2019). Clinic #1 is a general internal medicine clinic, clinic #2 is a community-based family medicine clinic, and clinic #3 is a multi-specialty clinical practice that includes family medicine as well as other specialty clinics. In clinic #3, the program was also available in two specialty clinics - cardiology and gastrointestinal medicine (GI)- in addition to primary care. Between 2019 and 2020, 109 providers practiced in clinic #1, 42 in clinic #2, and 20 in clinic #3 (Table 5). All providers practicing in the pilot clinics were eligible to order the PopHealth genomic screening test for their patients.

Over the period from July 10, 2018 to December 07, 2020, a total of 929 PopHealth tests were ordered by 56 providers across the 3 pilot clinics. Clinic #1 had the most providers who ordered the test (n = 38, adoption rate = 34.8% (38/109)); clinic #2 had 14/42 (33.3%) providers who ordered the test, and clinic #3 had 3/20 (15.0%). The overall provider-level adoption rate in the 3 pilot clinics was 56/171 (32.7%) (Table 5). Of the 56 providers who ordered the PopHealth test at least once, 27 (48.2%) were physicians, 26 (46.4%) were trainees (fellows or residents), and 3 (5.4%) were advanced health practitioners (including certified nurse practitioners and physician assistants) (Table 5). A majority of residents (18/23) who ordered the test were attended by physicians who also had a history of ordering the test, however there were a few instances (5/23) where a resident ordered the test without an attending physician who also had utilized the test.

Table 5. Number and Percentage of Providers that Ordered PopHealth, and the Number of Tests Ordered Per Provider in 3 Pilot Clinics

Clinic	Clinic Type	Total # of providers	Number of Providers who ordered PopHealth Test, n				Adoption Rate	Number of tests ordered per provider, median [min, max]			
			Total	Stratified by provider type				Total	Stratified by provider type		
				Physician	Trainee	AP			Physician	Trainee	AP
Clinic #1	General Internal Medicine	109	38	20	16	2	34.8%	2 [1, 142]	7 [1, 142]	1 [1,2]	3.5 [1,6]
Clinic #2	Family Medicine	42	14	4	9	1	33.3%	8 [1, 464]	6 [2, 464]	8 [1,21]	17[17,17]
Clinic #3	Family Medicine, Cardiology and GI	20	3	3	-	-	15.0%	14 [5, 32]	14 [5, 32]	-	-
Unknown			1	-	1	-		1 [1, 1]	-	1 [1,1]	-
Total		171	56	27	26	3	32.7%	2 [1, 464]	8 [1, 464]	1.5 [1, 21]	6 [1, 17]

Abbreviation: AP, Advanced Practitioner.

The level of adoption among the providers was highly variable. A majority of the providers who ordered the test (42/56, 75%) ordered fewer than 10 tests, and 29 (51.8%) only ordered 1 or 2 tests (Figure 3). One high utilizing provider ordered almost half of the total amount of tests (464/929, 49.9%), and the second highest utilizing provider ordered 142 (15.3%) (Figure 3). Compared by provider type, physicians generally ordered more tests than other types of providers (median [range]: 8 [1,464] compared to 1.5[1, 21] by fellows/residents, and 6 [1,17] by advanced health practitioners) (Table 5).

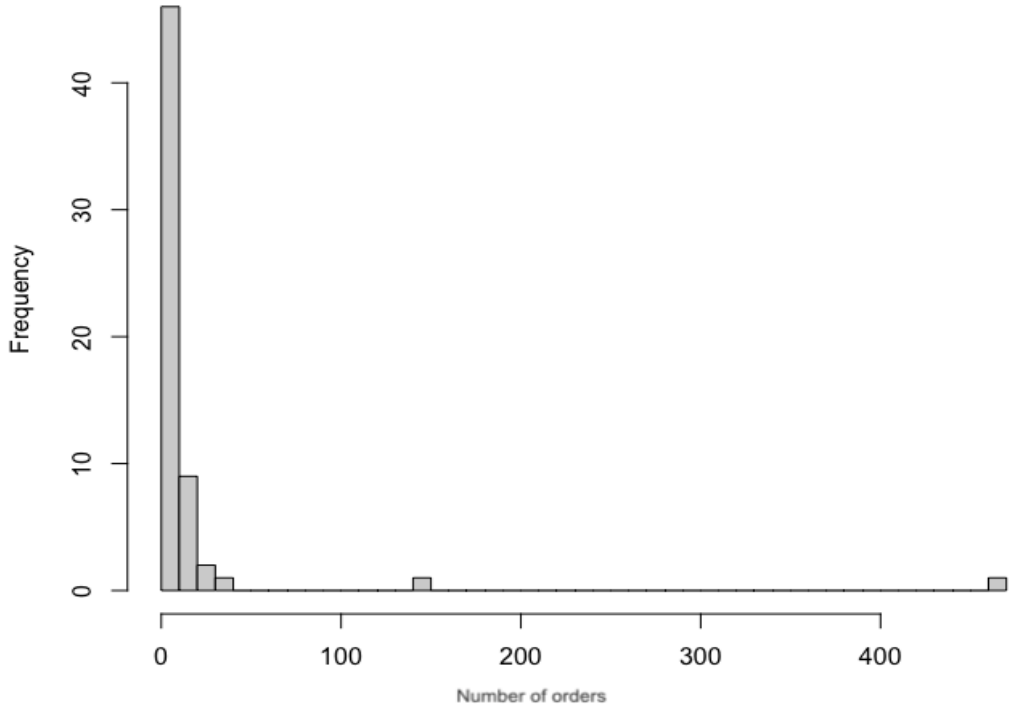


Figure 3. Distribution of Providers by the Number of Tests Ordered

4.4 Implementation

Implementation consistency was only assessed among the 14/56 providers who ordered the PopHealth test more than 10 times. The test was consistently offered with an average of 1.9 tests per provider per month (Figure 5). High utilizing provider #1 ordered on average 16.6 ± 15.1 tests per month, with a spike between 6 -12 months after the PopHealth program was implemented in that clinic. High utilizing provider #2 ordered an average of 5.5 ± 4.1 tests per month, and the number of tests ordered per month was relatively consistent (Figure 6).

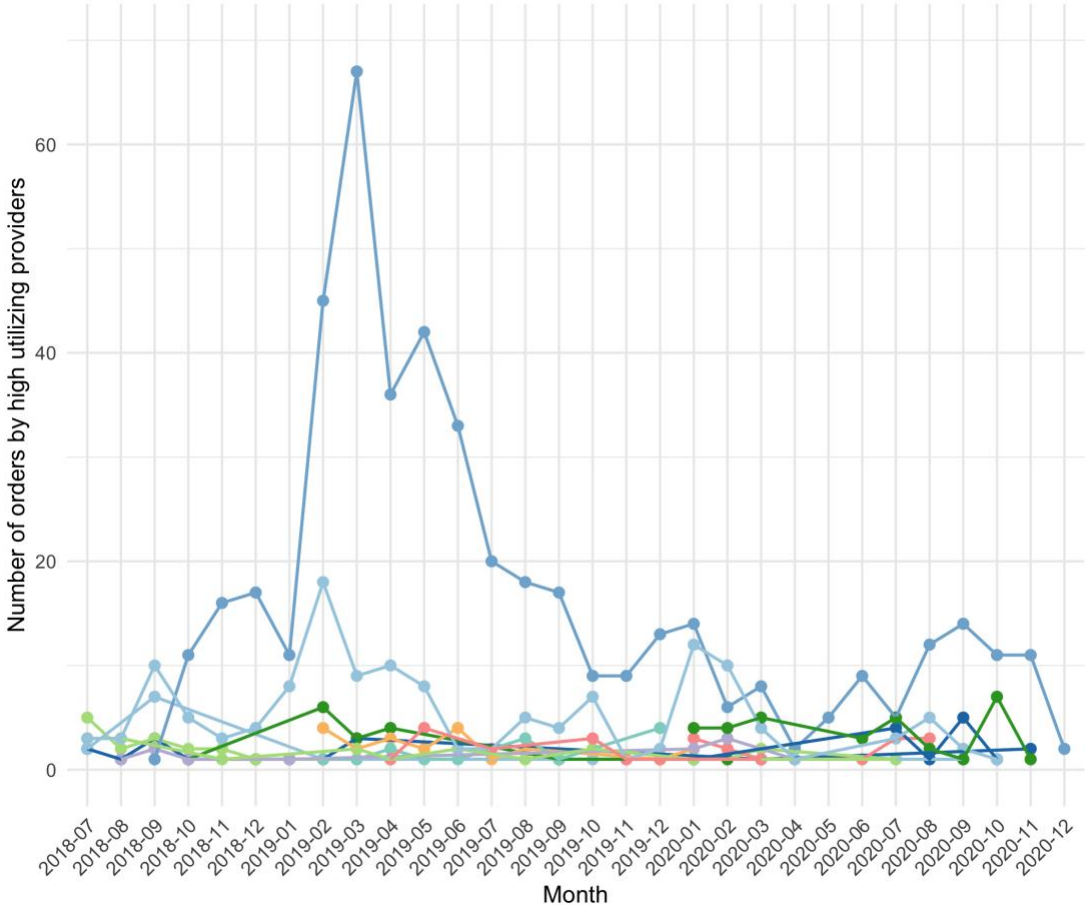


Figure 4. Number of Tests Ordered by 14 High-utilizing providers by Month

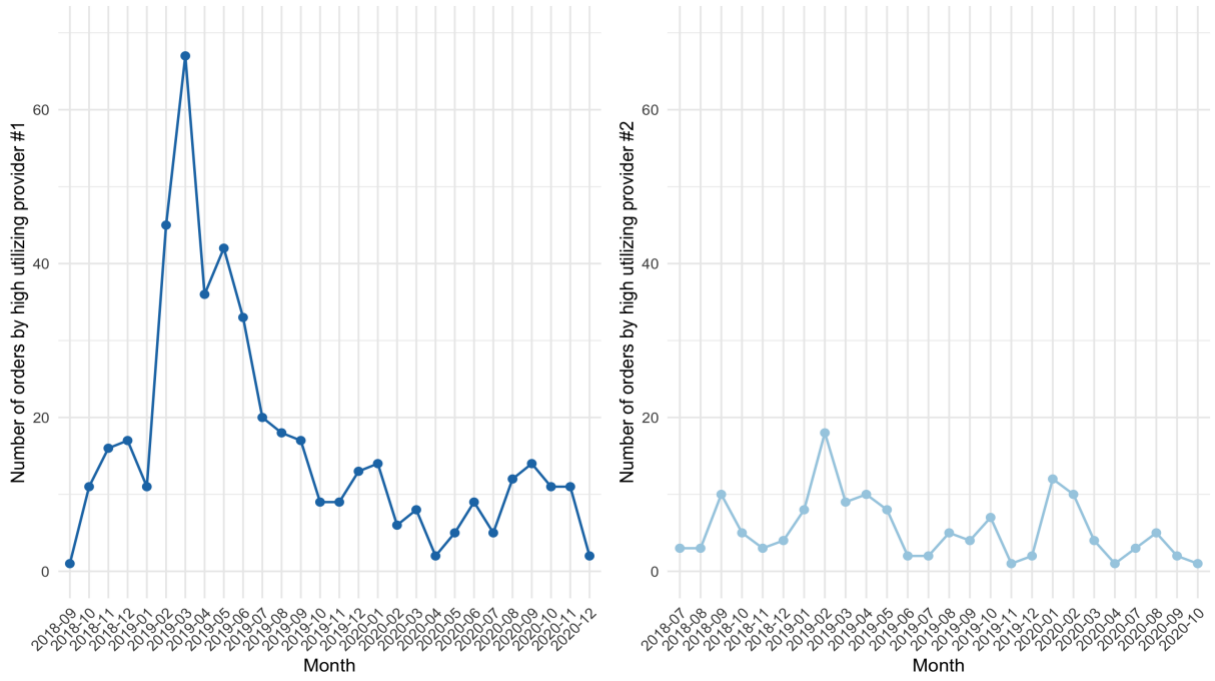


Figure 5. Number of Tests Ordered by High-utilizing Providers #1 and #2 By Month

Of the 14 providers who ordered PopHealth more than 10 times, 12 (85.7%) used Epic SmartSet for >80% of the tests they ordered for patients. Of the 2 providers who did not consistently use Epic SmartSet, one provider (high utilizing provider #2) only used SmartSet 4% of the time, and the other used it 61% percent of the time.

4.5 Maintenance

Besides the one spike six months after the program was implemented in clinic #2, the test was consistently offered since becoming available in the three pilot clinics with some month-to-month variations (Figure 6). The spike overlaps with the trend in test orders by high utilizing provider #1 (Figure 5), meaning the spike was likely driven by a single provider.

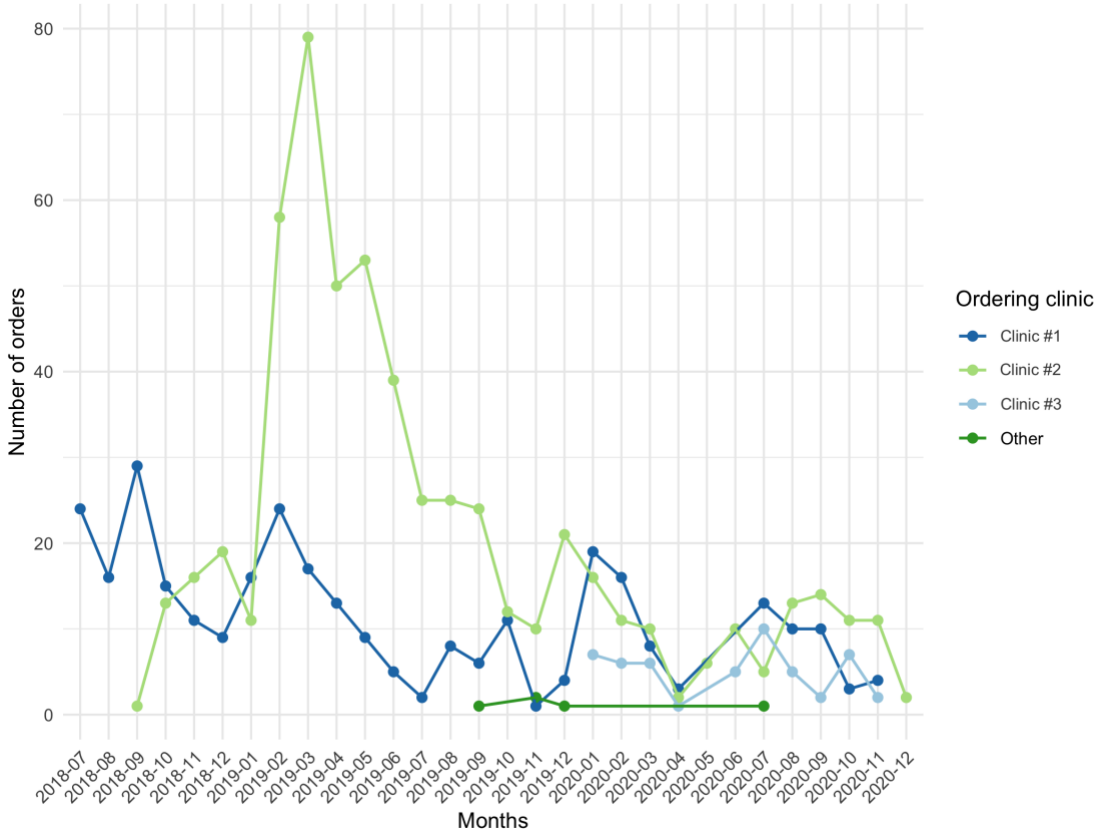


Figure 6. Nnumber of Tests Ordered by Month, By Clinic

5.0 Discussion

Population-based genomic screening holds great promise in improving ascertainment of individuals at genomic risk for serious but medically actionable conditions. However, before population-based genomic screening can be implemented broadly as a routine clinical practice, many questions remain to be addressed about its clinical utility, implementation feasibility, sustainability, and potential public health impact[12,13]. By evaluating the implementation outcomes of population-based genomic screening programs in an integrated health system, this project generates several valuable insights that can inform these questions.

We found that the program was able to reach a significant portion of the target population, as more than two-thirds of the approached Geisinger patients were willing to participate in the MyCode program and receive genomic results. The rate of participation in the program was significantly influenced by participants' age, sex and race/ethnicity. Participants in MyCode were predominantly white and non-Hispanic, which can be partially attributed to the racially and ethnically homogeneous population in the Geisinger service area. However, compared to the general Geisinger patient population, participants of genomic screening were even less diverse in terms of race and ethnicity, suggesting that race/ethnicity may play a role in patient's willingness to participate in the program. We also found that individuals willing to participate in the program had significantly higher utilization of Geisinger PCPs and the Geisinger Health Plan, suggesting that the program is more likely to reach the population that has established a patient-provider relationship with the health system.

Previous studies on the clinical utility of the MyCode Genomic Screening and Counseling program have indicated the program's ability to identify individuals unaware of their genomic risk

for CDC Tier 1 conditions, facilitate risk management and potentially improve their clinical outcomes[17–20,67,68,84,85]. These studies also provided evidence regarding the prevalence and penetrance of Tier 1 variants in the population unselected for medical indications. More research efforts are currently underway to extend the investigation to conditions outside of Tier 1. Together, these findings can help inform the overall clinical utility of screening unselected populations for genomic risk variants.

Our findings also demonstrated the feasibility of integrating population-based genomic screening into the clinical setting. The PopHealth clinical genomic screening test has been implemented in three primary care and specialty clinics, and has generated clinical screening reports for almost 1,000 participants. However, the screening test has not been universally adopted by all providers in clinics where the program is available. Only a minority of the eligible providers in the pilot clinics have ordered the test for patients, and fewer have ordered the test consistently. We found two attending physicians who ordered a majority of the tests and have led medical residents attended by them to also utilize the test, suggesting that successful implementation of population genomic screening program might depend on support from clinical champions.

This study also represents a unique utilization of the RE-AIM framework – to evaluate the implementation of a single program concept using data from different programs. The MyCode and PopHealth programs could be evaluated on their own; however, the biobank-based MyCode program cannot inform how genomic screening would be adopted and implemented in the clinical setting, and the PopHealth program has only been implemented in three pilot clinics with limited data generated regarding its reach to the patient population and its clinical benefit. Evaluating the data generated from these programs together as appropriate to the RE-AIM constructs can help us

understand the potential reach, effectiveness, and adoption of population-based genomic screening in the clinical setting within an integrated health system.

5.1 Limitations

This evaluation must be understood within the contextual limits of the data. We did not always have complete data for every component of the evaluation, and some constructs were operationalized in ways that do not fully capture the components being evaluated. For example, the *Reach* of the program ideally should be evaluated using both the proportion of individuals willing to participate in the PopHealth clinical screening program and the proportion of individuals willing to receive genomic results from MyCode. However, the data for individuals who were offered the PopHealth screening test were not available due to logistical limitations within the real-world clinical setting. Similarly, the individuals who declined participation in the MyCode biobank may also be under reported as not all individuals approached by consenters were recorded. Key informants of the program estimated that the number was likely to be under-recorded by 10-20%. Moreover, MyCode participants who consented before Return of Results was implemented were counted as non-participants for genomic screening, but it does not necessarily mean that these individuals were unwilling to participate in the screening program if it was offered to them, which further complicated the *Reach* estimation.

Furthermore, only limited data from the PopHealth program were available for the evaluation of the *Adoption* and *Implementation* constructs. Implementation consistency in the case of population-based genomic screening pertains to the degree to which providers consistently offered the test to primary care patients and whether they offered the test to patients without input

of medical indications. However, how providers offered the test and to which patients they offered it have not been documented due to logistical limitations. Current studies are underway to conduct semi-structured interviews with high-utilizing providers and PopHealth program leadership in order to gather more insights related to the *Adoption* and *Implementation* of the program, including the reasons why providers chose to order the test for their patients, how providers ordered the test, as well as barriers and facilitators of delivering the screening program in the primary care context.

Regarding the literature review for the *Effectiveness* construct, although we used a systematic method to review previous research findings, it is possible that not all relevant findings were adequately described or accurately coded. The research questions and types of data used can be condition-specific and varied across different studies, which created some challenges in synthesizing the findings in a consistent way. Moreover, some findings could be interpreted to address multiple themes in the codebook. A more systematic evidence synthesis method is needed to better review the clinical utility of the program.

There is also significant data gap in *Maintenance*. The cost of the screening test is currently covered by research finding, and we do not know whether the programs can be sustained once the funding is removed. On the individual level, most clinical outcomes of patient-participants have only been tracked for 1-2 years. More research is needed to understand the long-term outcomes of receiving a genomic result in this population.

5.2 Public Health Significance and Future Directions

To our knowledge, this is the first comprehensive program evaluation of population-based genomic screening programs. By using the RE-AIM framework to connect and evaluate the

different programs at Geisinger, we view the Geisinger programs as a laboratory for understanding the multi-level and complex implementation issues and informing the future implementation of population-based genomic screening on a larger scale.

We also present a model of using an implementation science framework to systematically assess and report key outcomes of population-based genomic screening programs. Reporting the implementation outcomes of the program systematically will provide us the opportunity to compare the outcomes from similar programs with respect to different implementation contexts and strategies, which will help improve our understanding of the barriers and facilitators of implementing such programs and facilitate the development of evidence-based implementation strategies.

Appendix A Supplementary tables and figures

Appendix Table 1. Existing and Geisinger's List for Returning Genomic Results

	Gene	Condition	ACMG 59[46]	Geisinger 76[26]	Geisinger 60[65]	CDC Tier 1[49]
1	*BRCA1*	Hereditary breast and ovarian cancer syndrome	✓	✓	✓	✓
2	*BRCA2*	Hereditary breast and ovarian cancer syndrome	✓	✓	✓	✓
3	*TP53*	Li-fraumeni syndrome	✓	✓	✓	
4	*STK11*	Peutz-jeghers syndrome	✓	✓	✓	
5	*MLH1*	Lynch syndrome	✓	✓	✓	✓
6	*MSH2*	Lynch syndrome	✓	✓	✓	✓
7	*MSH6*	Lynch syndrome	✓	✓	✓	✓
8	*PMS2*	Lynch syndrome	✓	✓	✓	✓
9	*APC*	Familial adenomatous polyposis	✓	✓	✓	
10	*MUTYH*	Familial adenomatous polyposis	✓	✓	✓	
11	*VHL*	Von Hippel Lindau syndrome	✓	✓	✓	
12	*MEN1*	Multiple endocrine neoplasia	✓	✓	✓	
13	*RET*	Multiple endocrine neoplasia	✓	✓	✓	
14	*PTEN*	Cowden syndrome 1	✓	✓	✓	
15	*RB1*	Retinoblastoma	✓	✓	✓	
16	*SDHD*	Hereditary Paraganglioma-pheochromocytoma Syndromes	✓	✓	✓	
17	*SDHAF2*	Hereditary Paraganglioma-pheochromocytoma Syndromes	✓	✓	✓	
18	*SDHC*	Hereditary Paraganglioma-pheochromocytoma Syndromes	✓	✓	✓	
19	*SDHB*	Hereditary Paraganglioma-pheochromocytoma Syndromes	✓	✓	✓	
20	*TSC1*	Tuberous sclerosis complex	✓	✓	✓	
21	*TSC2*	Tuberous sclerosis complex	✓	✓	✓	

	Gene	Condition	ACMG 59[46]	Geisinger 76[26]	Geisinger 60[65]	CDC Tier 1[49]
22	*WT1*	WT-1 related Wilms tumor	✓	✓	✓	
23	*NF2*	Neurofibromatosis, type2	✓	✓	✓	
24	*COL3A1*	Vascular Ehlers-danlos syndrome	✓	✓	✓	
25	*FBN1*	Marfan syndrome	✓	✓	✓	
26	*TGFBR1*	Loeys-dietz syndrome	✓	✓	✓	
27	*TGFBR2*	Loeys-dietz syndrome	✓	✓	✓	
28	*SMAD3*	Loeys-dietz syndrome	✓	✓	✓	
29	*ACTA2*	Familial Thoracic Aortic Aneurysms and Dissections	✓	✓	✓	
30	*MYLK*	Familial Thoracic Aortic Aneurysms and Dissections		✓		
31	*MYH11*	Familial Thoracic Aortic Aneurysms and Dissections	✓	✓	✓	
32	*MYBPC3*	Cardiomyopathy	✓	✓	✓	
33	*MYH7*	Cardiomyopathy	✓	✓	✓	
34	*TNNT2*	Cardiomyopathy	✓	✓	✓	
35	*TNNI3*	Cardiomyopathy	✓	✓	✓	
36	*TPM1*	Cardiomyopathy	✓	✓	✓	
37	*MYL3*	Cardiomyopathy	✓	✓	✓	
38	*ACTC1*	Cardiomyopathy	✓	✓	✓	
39	*PRKAG2*	Cardiomyopathy	✓	✓	✓	
40	*GLA*	Cardiomyopathy	✓	✓	✓	
41	*MYL2*	Cardiomyopathy	✓	✓	✓	
42	*LMNA*	Cardiomyopathy	✓	✓	✓	
43	*DES*	Cardiomyopathy		✓		
44	*PLN*	Cardiomyopathy		✓		
45	*RYR2*	Catecholaminergic polymorphic ventricular tachycardia	✓	✓	✓	
46	*PKP2*	Arrhythmogenic right ventricular cardiomyopathy	✓	✓	✓	
47	*DSP*	Arrhythmogenic right ventricular cardiomyopathy	✓	✓	✓	

	Gene	Condition	ACMG 59[46]	Geisinger 76[26]	Geisinger 60[65]	CDC Tier 1[49]
48	*DSC2*	Arrhythmogenic right ventricular cardiomyopathy	✓	✓	✓	
49	*TMEM43*	Arrhythmogenic right ventricular cardiomyopathy	✓	✓	✓	
50	*DSG2*	Arrhythmogenic right ventricular cardiomyopathy	✓	✓	✓	
51	*JUP*	Arrhythmogenic right ventricular cardiomyopathy		✓		
52	*TGFB3*	Loeys-dietz syndrome		✓		
53	*KCNQ1*	Inherited arrhythmias	✓	✓	✓	
54	*KCNH2*	Inherited arrhythmias	✓	✓	✓	
55	*SCN5A*	Inherited arrhythmias	✓	✓	✓	
56	*CACNA1C*	Inherited arrhythmias		✓		
57	*CACNB2*	Inherited arrhythmias		✓		
58	*CAV3*	Inherited arrhythmias		✓		
59	*GPD1L*	Inherited arrhythmias		✓		
60	*HCN4*	Inherited arrhythmias		✓		
61	*KCNE1*	Inherited arrhythmias		✓		
62	*KCNE2*	Inherited arrhythmias		✓		
63	*KCNE3*	Inherited arrhythmias		✓		
64	*KCNJ2*	Inherited arrhythmias		✓		
65	*SCN1B*	Inherited arrhythmias		✓		
66	*SCN3B*	Inherited arrhythmias		✓		
67	*SCN4B*	Inherited arrhythmias		✓		
68	*SNTA1*	Inherited arrhythmias		✓		
69	*LDLR*	Familial hypercholesterolemia	✓	✓	✓	✓
70	*APOB*	Familial hypercholesterolemia	✓	✓	✓	✓
71	*PCSK9*	Familial hypercholesterolemia	✓	✓	✓	✓
72	*RYR1*	Malignant hyperthermia	✓	✓	✓	
73	*CACNA1S*	Malignant hyperthermia	✓	✓	✓	

	Gene	Condition	ACMG 59[46]	Geisinger 76[26]	Geisinger 60[65]	CDC Tier 1[49]
74	*ENG*	Hereditary hemorrhagic telangiectasia		✓		
75	*ACVRL1*	Hereditary hemorrhagic telangiectasia		✓		
76	*OTC*	Ornithine transcarboxylase deficiency	✓	✓	✓	
77	*ATP7B*	Wilson disease	✓		✓	
78	*BMPR1A*	Juvenile polyposis	✓		✓	
79	*SMAD4*	Juvenile polyposis/hereditary hemorrhagic telangiectasia	✓		✓	
80	*HFE*	Hemochromatosis			✓	

Appendix Table 2. Published Studies Relevant to the Effectiveness of MyCode GSC

Author(year)	Condition	Study Sample	Key Finding	Theme
Abul-Husn (2016), Science[17]	FH	DiscovEHR (N = 50,726)	229/50,726 individuals carried one of the P/LP FH variants.	Prevalence
		DiscovEHR (N = 50,726)	Individuals with an FH variant had increased odds of CAD compared to noncarriers [odds ratio (OR), 2.6; 95% confidence interval (CI), 2.0 to 3.5; $P = 4.3\times10^{-11}$].	Penetrance
		Patient-participants from DiscovEHR cohort who were identified as FH variant carriers and were living (n = 215)	172/215 patients who did not meet DLCN criteria for FH without the genomic result meet criteria for a definite FH diagnosis with genomic result.	Ascertainment; Clinical outcome
		Patient-participants from DiscovEHR cohort who were identified as FH variant carriers and were living (n = 215)	75/215 were deemed as unlikely to have FH based on EHR without the input of genomic result (DLCN < 3). The variants carried by these patients were considered to have reduced penetrance.	Penetrance
Buchanan (2017), Genetics in Medicine[18]	HBOC	Patient-participants who were notified of their clinical confirmed P/LP BRCA 1/2 variant before April 2017 (n = 55)	79% (26/33) of the patient-participants who were eligible for risk management had performed at least one risk management procedure.	Risk management
		Patient-participants who were notified of their clinical confirmed P/LP BRCA 1/2 variant before April 2017 (n = 55)	11/55 individuals had personal history of BRCA1/2 related cancer but were unaware of their genomic variant. 37/55 had no prior knowledge of their variant and no compelling family history of HBOC. 3 were found to have early-stage cancer via post-RoR risk management within a year of result disclosure.	Ascertainment; Clinical outcome
McCormick (2017)[85] Abstract in APHA Meeting	HBOC, LS, FH	DiscovEHR (N = 50,726)	P/LP variants in the 10 target genes associated with HBOC, LS and FH were found in 650/50,726 participant samples. An aggregate prevalence of 1:78 (1.28%) for the 3 conditions was observed.	Prevalence

Author(year)	Condition	Study Sample	Key Finding	Theme
Genomics Forum	HBOC	First 128 cases with P/LP BRCA1/2 results clinically confirmed and returned	15% had prior clinical testing, an additional 15% had relevant clinical disease.	Penetrance
Manickam (2018), JAMA[20]	HBOC	DiscovEHR (N = 50,726)	267/50,726 individuals had a P/LP variant in BRCA 1/2, out of which 183 received their clinical confirmed results. The prevalence of P/LP BRCA variants in this population was 1:190.	Prevalence
		Patient-participants from DiscovEHR cohort who were identified as BRCA1/2 carriers (n = 267)	Only 17.9% (48/267) of the BRCA1/2 carriers were aware of their variant from prior clinical genetic testing.	Ascertainment
		Patient-participants from DiscovEHR cohort who were identified as BRCA1/2 carriers (n = 267)	In 89 cases with available personal and family health history but who did not have prior testing for BRCA1/2, 50.5% (45/89) meet NCCN criteria for testing.	Ascertainment
		Patient-participants from DiscovEHR cohort who were identified as BRCA1/2 carriers (n = 267)	20.9% (56/267) of the BRCA1/2 identified carriers had a prior syndromic cancer diagnosis.	Penetrance
Jones (2018)[84] Circulation: Genomic and Precision Medicine	FH	Patient-participants who received a P/LP result in one of the FH genes from June 2015 to July 2016 and had adequate EHR (n = 23)	Within a median of 1.32 years of post-disclosure follow-up, 80% (19/23) of the patient-participants discussed their result with a health professional; 23% (9/23) patient-participants had changes made to their treatment regimens	Risk management
		Patient-participants who received a P/LP result in one of the FH genes from June 2015 to July 2016 and had adequate EHR (n = 23)	3 patient-participants who did not met the lipid level control goal (LDL-C < 100mg/dL) before learning their results met goal after result disclosure and risk management.	Clinical outcome
		Patient-participants who received a P/LP result in one of the FH	Most participants were not surprised by their result as all knew they had high cholesterol and/or family history of	Psychosocial outcome

Author(year)	Condition	Study Sample	Key Finding	Theme
		genes from June 2015 to July 2016 and participated in semi-structured interview (n = 7)	CAD; 2 felt that the genomic result provided an answer to their personal or family history. One unexpected nonpaternity was found.	
Hao (2020) Journal of Personalized medicine[67]	HBOC	Female patient-participants who received P/LP BRCA1/2 results from MyCode before March 2016 and had no personal breast or ovarian cancer diagnosis (n =59)	Within the first year after result disclosure, 29/59 women had a genetic counseling visit, 29/58 eligible patients had mammogram or MRI, 2/57 had mammogram, 6/51 had oophorectomy.	Risk management
		Female patient-participants who received P/LP BRCA1/2 results from MyCode before March 2016 and had no personal breast or ovarian cancer diagnosis (n =59)	No statistically significant differences in inpatient and outpatient utilization and average total costs were found between one-year pre- and one-year post-disclosure periods ($18,821 vs. $19,359, p = 0.76).	Financial outcome
Buchanan (2020)[19] Genetics in Medicine	HBOC, LS, FH	Patient-participants with a P/LP results in Tier 1 conditions disclosed between May 2015 to February 2018 who were unaware of their genetic variant (n = 305)	65% had EHR evidence of a personal or family history of relevant disease	Penetrance
		Patient-participants with a P/LP results in Tier 1 conditions disclosed between May 2015 to February 2018 who were unaware of their genetic variant (n = 305)	Of 15 individuals without prior knowledge of their genetic result in HBOC and LS had a relevant cancer diagnosis, 53% (8/15) attributed the diagnosis to MyCode result disclosure; 26 individuals with FH risk variants who were unaware of their condition had a post disclosure diagnosis for FH. 65% (17/26) attributed the diagnosis to MyCode result disclosure; Collectively 61% (25/41) attributed diagnoses to genomic result disclosure.	Clinical outcome
		Patient-participants with a P/LP results in Tier 1 conditions disclosed between May 2015 to	Out of 255/305 patient-participants who were eligible for risk management, 48.2% (123/255) had risk management before result disclosure, and 70.2% (179/255) had risk management post-disclosure, which include 75	Risk management

Author(year)	Condition	Study Sample	Key Finding	Theme
		February 2018 who were unaware of their genetic variant (n = 305)	individuals who had not had any risk management before and started risk management post-disclosure	
Jones (2020)[68] Abstract in Journal of Clinical Lipidology	FH	Patient-participants who received a P/LP result in FH, had insurance coverage, and filled at least one LLT prescription after result disclosure (n = 18)	There was a statistically significant improvement in LLT adherence post-disclosure (Mean (SD), 76.8% (27.5%)) compared to pre-disclosure (63.9% (30.3%), p=0.01).	Risk management

Abbreviation: FH, familial hypercholesterolemia; CAD, Coronary artery disease; LS, Lynch syndrome; LLT, Lipid-lowering therapy.

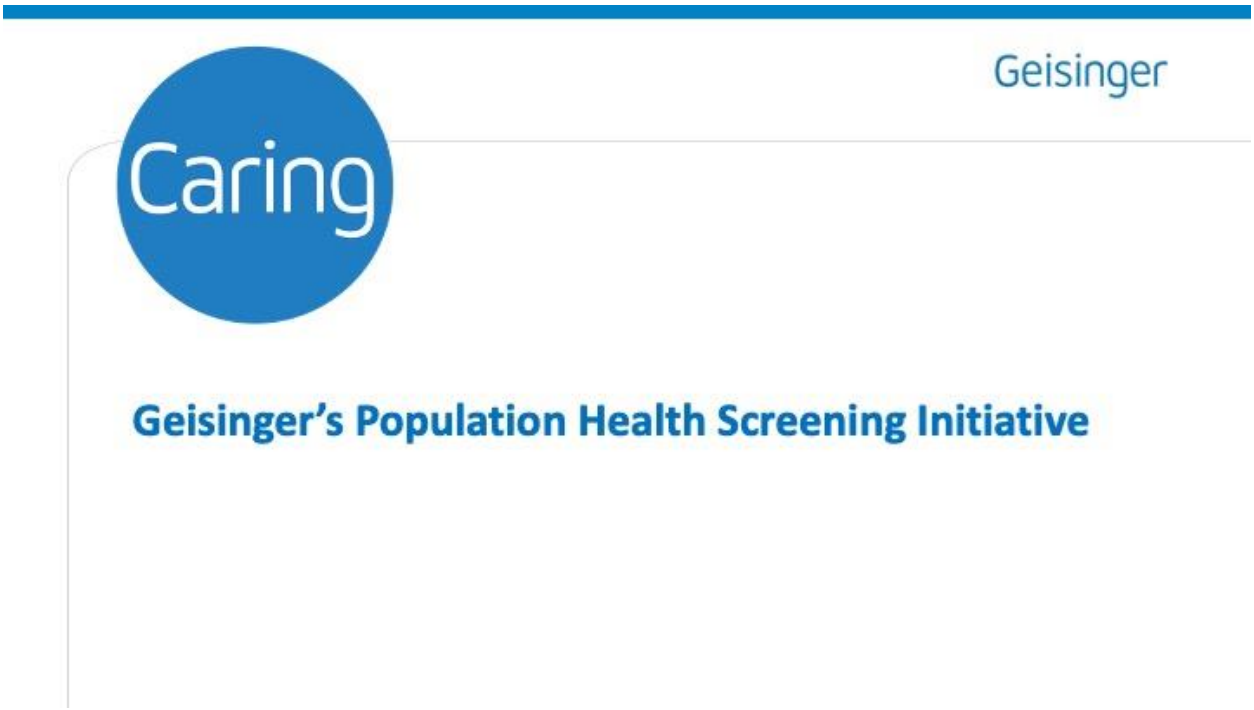
Appendix Table 3. Ongoing Projects Related to Effectiveness of MyCode GSC

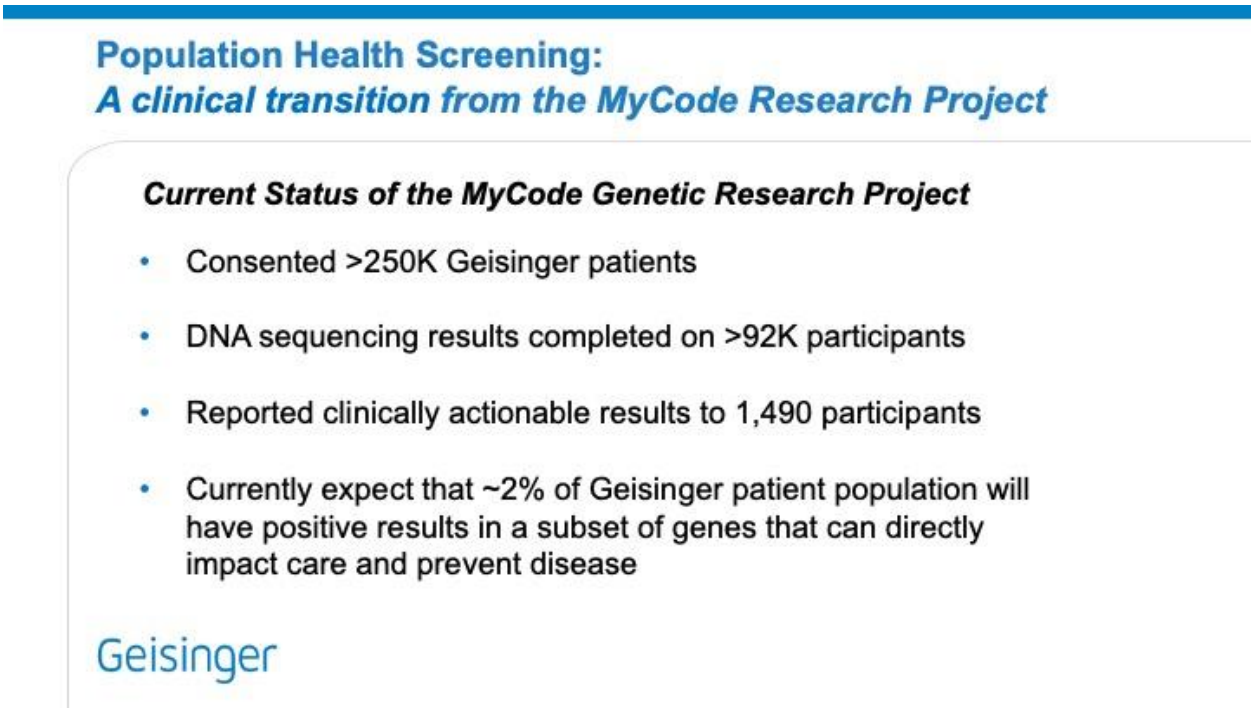
Subject/Title	Condition	Methods	Study Sample	Key Questions	Theme
Colon and uterine cancer incidence in LS cases identified by population screening	Lynch syndrome	Retrospective chart review	Patient-participants identified through MyCode exome sequences (N = 87,493) to have P/LP variants in one of the MMR genes AND who have provided a pedigree (n = 113)	What are the incidence and family histories of LS related cancers in individuals identified to have P/LP LS variants through MyCode? Do they meet clinical NCCN guidelines for LS testing?	Penetrance Ascertainment
Experience completing population screening for variants associated with endocrine tumor syndromes in a large, healthcare-based cohort	Endometrial tumor syndrome (ETS)	Retrospective chart review	Patient-participants identified from available MyCode exome sequences (N = 87,493) to have P/LP variants in one of the ETS related genes	What percentage of patients ascertained through MyCode GSC had a personal or family history indicative of the endocrine tumor syndrome associated with the variant identified? After identification of a pathogenic/likely pathogenic variant in a gene associated with endocrine tumor syndrome, are patients altering medical management?	Penetrance Risk management
APC Variants	Familial adenomatous polyposis	Retrospective chart review	-	What is the penetrance of phenotype in individuals with P/LP APC variants ascertained through population screening?	Penetrance

Subject/Title	Condition	Methods	Study Sample	Key Questions	Theme
Cardiovascular Phenotypes	Cardiovascular diseases (ARVC, cardiomyopathy)	Retrospective chart review	-	Are patient-participants with cardiovascular risk variants identified through MyCode aware of their genetic cardiovascular risk? What is the penetrance of cardiovascular disease in patients identified through MyCode; does penetrance vary by gene or variant type?	Ascertainment Penetrance
Malignant Hyperthermia	Malignant Hyperthermia	Retrospective chart review	Patient-participants identified from the 145k cohort	What is the phenotypic presentation of MH in patient-participants ascertained through MyCode? What percentage of first-degree relatives have reported MH-related phenotypes?	Penetrance
Cascade testing, family communicating and family sharing	All	Survey		What is the cascade testing uptake of patient ascertained through MyCode? What are the reasons that probands give for sharing their results to family? Any decisional regret or positive/negative emotions?	Risk Management Psychosocial outcomes
Non-core cancers in BRCA1/2 carriers	BRCA1/2 related cancers	Retrospective chart review		What is the rate of "non-core" cancers in BRCA1/2 carriers compared to controls? Are there any specific types of cancer with a statistically significant difference in risk?	Penetrance

Subject/Title	Condition	Methods	Study Sample	Key Questions	Theme
Hemochromatosis	Hemochromatosis	Retrospective chart review	Patient-participants identified from 90k cohort	Percentage of individuals ascertained through MyCode screening who had personal or family history of hemochromatosis or HFE related diagnosis	Penetrance

Appendix B PopHealth Training Materials for Providers





Primary Care Physicians push transition to clinical care

- Dr. Burke's 87 year old patient, Donna, found to have a pathogenic change in *BRCA2*
- How useful is this information to Donna?
- She has two daughters and one son…

"When she brought her daughters in for screening, I realized this test is *not just screening for the patient*, but finding something that *impacts the whole family*…
I'm thinking about that a lot more now."

(Dr. Burke has had 14 patients with positive MyCode results.)

Dr. Greg Burke
Geisinger Internal Medicine
Chief Patient Experience Officer

3

Clinical Whole Exome Sequencing - Population Health Screening

- Launched July 10th – 1st patient

Dr. David T. Feinberg reveals health system's pioneering precision health efforts will be recommended to every patient

LAS VEGAS – Mammograms, colonoscopies and cholesterol checks are just a few of the routine screenings saving lives by detecting cancers and heart disease early.

Geisinger patients will soon add DNA sequencing to that list.

Geisinger President and CEO David T. Feinberg, M.D., MBA, announced Sunday that the Pennsylvania-based health system is expanding its successful genomics program beyond the realm of research and into everyday, preventive care.

Geisinger President and CEO Dr. David Feinberg

Moving DNA sequencing from research to the clinic

	mycode	Clinical Genetics Services	Population Health Screening
Purpose	**Research Study**	**Referral Based Service for Personal/Family Hx of Concern**	**New Clinical Screening Test for Primary Care**
Scope	Discovery with return of results for selected well-described genes	Varies per indication *cancer, autism, arrhythmia…*	ACMG secondary finding 59-gene panel **primarily cancer, cardiac genes*
How to order it?	Provider cannot order; Must consent for study.	Clinical Test determined by specialty area *General genetics, oncology, prenatal*	Clinical Test *Population Health Whole Exome Screening (PWES)*
Timeline	Ongoing - may be years	Most panels ~3 weeks; *Some tests STAT (1-2 days)*	6-8 weeks
Test Reports	POSITIVE reports only NEGATIVES not reported	Complete Diagnostic Report	Complete Screening Report

Population Health Screening: *GOALS*

- *Anticipatory care for disease prevention* instead of reactionary treatment
- *Earlier detection* of disease to enable better management and improved outcomes
- *More reliable identification of risk for patients and their families* to develop diseases like:
  - Hereditary breast and ovarian cancer
  - Lynch cancer syndrome
  - Familial hypercholesterolemia
  - Cardiac arrhythmias

Geisinger

Why are we launching this as a clinical test?

Example cases from the MyCode research project

- *BRCA2* – pathogenic change in patient with no evidence of disease yet ---

  "I feel like I cheated cancer."

- BRCA1/2 genes – Early-stage cancer diagnoses ---
  - 56yo woman: ductal carcinoma *in situ* detected on surveillance breast MRI
  - 55yo man: elevated PSA & positive prostate biopsy
- *KCNQ1* – pathogenic change found in patient, then two young sons who both have clinical symptoms of Long QT syndrome (LQTS). Boys on beta-blockers ---

  "I thank God for this program, that this [mutation] was found and I'm not burying one of my kids."

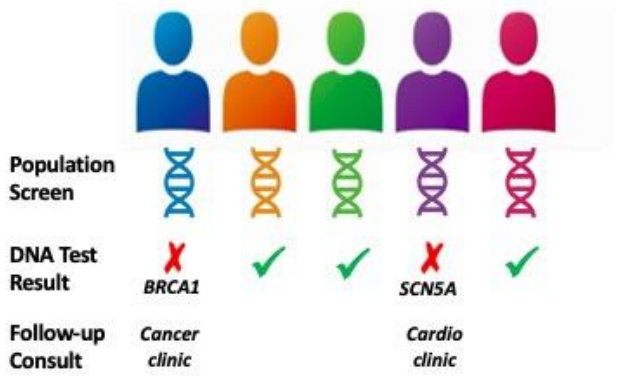
- Clinical work-up that followed genetic results disclosure – Life Saving!

Geisinger

mycode

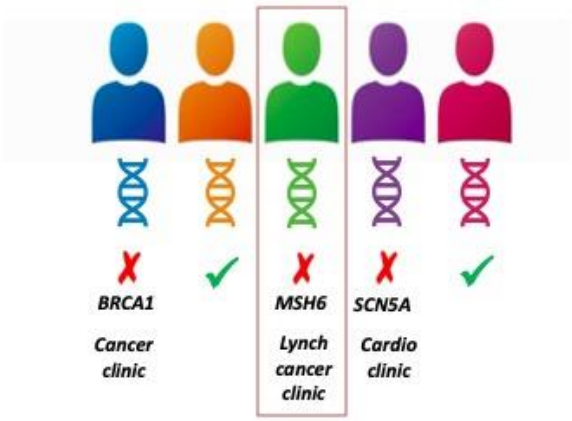
We can provide more targeted preventive care now

2018



Over time, we can update results

2020



Report updated on results from same sample based on new understanding and insights

Population Health Screening: *Which patients are eligible?*

- Adult Geisinger patients with ***ANY*** insurance type
- Limited number of clinics for pilot
  - General Internal Medicine in Danville
  - Kistler Clinic in Wilkes-Barre
  - Gray's Woods: Family Practice, Cardiology, Gastroenterology
- Any adult patient can be offered a brochure.
- There is **no cost** to the patient for this genetic testing, blood draw, or any genetic counseling if positive screen result (covered by pilot funds)
- *Encourage patients to have blood drawn promptly to ensure inclusion in pilot program*

Geisinger

Population Health Screening: *Check-in Staff Script*

- Geisinger is offering a new test to all adult patients which allows us to identify some genetic risks that you may have for developing diseases, such as cancer or heart disease.
- We are currently piloting this test in this clinic. This test is available to you today with no copayment, deductible, or coinsurance.
- This brochure will give you more information about the test. Please read the brochure and take it into your appointment. Your provider will know that you are eligible for this test when they see that you have the brochure.

Geisinger

Population Health Screening:
Epic SmartSet for Patient Information, Verbal Consent, Test Order & Result

Patient Information:

- Geisinger is offering a new test to adult patients to look for changes in your genes that might increase your risk for developing certain diseases, such as cancer or heart disease. This test might also find a genetic cause for a disease you already have.
- Although we each have thousands of genes, this test currently only looks for changes in about 60 genes.
- If you have a change that increases your risk for disease, you will be contacted by a member of our team to explain your results and how this information may be used to take care of you and your family members.
- If your testing does not show any gene change, it does not exclude all possible genetic causes for diseases you may have or develop in the future.
- Our main goal is to identify gene changes that increase your risk for a disease BEFORE you develop symptoms and use this information to better guide your medical management and keep you healthy.
- Currently, this test is available to you with no copayment, deductible, or coinsurance.

Population Health Screening:
Epic SmartSet for Patient Information, Verbal Consent, Test Order & Result

Verbal Consent:

- Would you like to have this test? If so, your verbal consent acknowledges your understanding of the written information, what we've discussed, and your voluntary approval to proceed with this clinical testing.
  □ verbal consent obtained □ test declined □ other

Test Order:

- 14489 – Population Health Whole Exome Sequencing Screening; PWES
- Z13.79 Genetic Screening

Result Reporting:

- Negative screen results – sent to provider through Epic – just like other normal test results; patient letter attached to lab results explains negative screen result
- Positive screen results – reviewed by genetics team, ordering physician informed of result; patient consult with appropriate genetics specialty; results uploaded into Epic

Privacy and Genetic Discrimination

- Governed by the same privacy laws as other clinical laboratory tests
- The Genetic Information Nondiscrimination Act (GINA)
  - A **federal law** that makes it illegal for health insurance companies, group health plans, and employers to obtain or use genetic information to take adverse actions
  - GINA **does not** prevent companies that sell life, disability, or long-term care insurance from requiring genetic information, including family history, to determine coverage or rates

Geisinger

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